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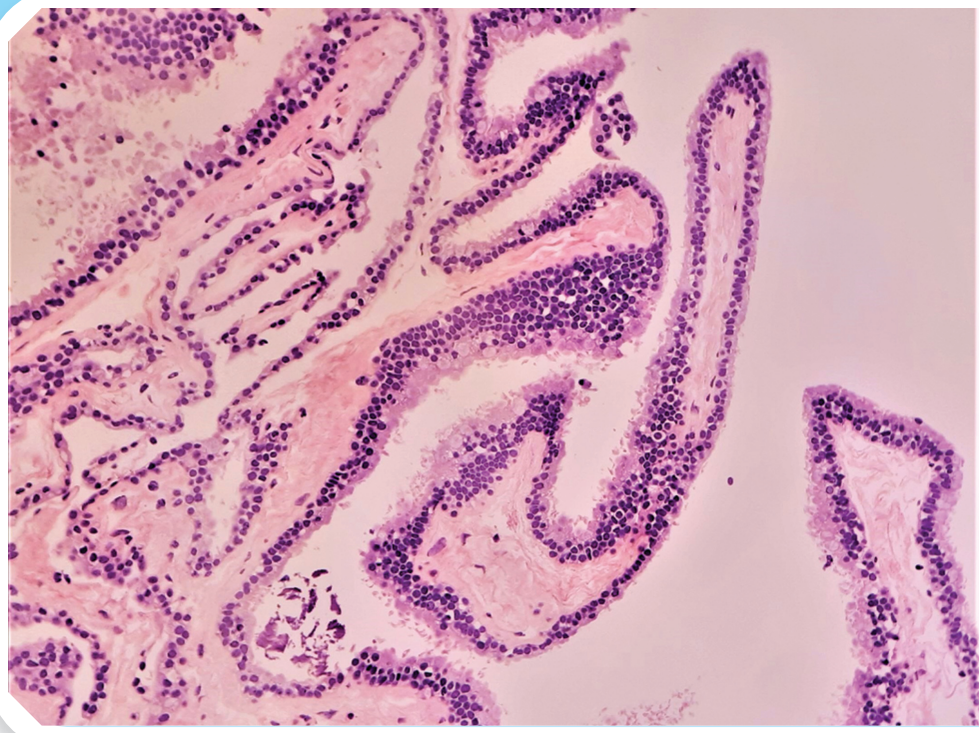

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Endoscopic Transsphenoidal Surgery of Pituitary Adenomas: Preliminary Results of the Neurosurgery Service of Hospital Cristo Redentor

Cirurgia endoscópica transesfenoidal de adenomas pituitários: resultados preliminares do Serviço de Neurocirurgia do Hospital Cristo Redentor

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Abstract

Objective The transsphenoidal surgery is a safe and effective technique to manage different skull base pathologies, such as pituitary adenomas. The purpose of the present study is to describe the initial experience with endoscopic transsphenoidal surgery in the treatment of pituitary adenoma patients at a tertiary hospital that is a reference in neurosurgery in Southern Brazil.

Materials and Methods We retrospectively analyzed data from 60 patients with pituitary adenoma who underwent endoscopic transsphenoidal surgery between 2012 and 2019. Demographic characteristics, type of tumor, baseline hormonal changes, and clinical presentation were reported, as well as postoperative outcomes, tumor resection rate, and complications.

Results The male/female ratio was of 0.53:1, and the mean age of the sample was of 54 (range: 26 to 79) years. In total, 34 patients (57%) presented the non-functioning adenoma subtype, and 26 (43%), the functioning adenoma subtype. In the non-functioning and functioning subtype groups, the average tumor diameter was of 32 mm and 18 mm, and the mean follow-up was of 27 months and 32 months respectively. Regarding visual symptoms, 79% of the patients showed improvement after surgery. Hormonal remission was achieved in 71% of the patients with

Keywords
- endoscopic surgery
- pituitary gland
- epidemiology
- adenoma

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prolactinoma, 85% of those with cushing, and 57% of patients with acromegaly. Overall, gross total resection (GTR) was achieved in 50% of patients but with a significantly lower rate among patients with tumors with parasellar growth (high grade on the Knosp classification). The most prevalent surgical complications observed were postoperative cerebrospinal fluid (CSF) leak and meningitis in 11% and 6% of the cases respectively.

Conclusion We have shown that transsphenoidal endoscopic surgery can produce good results in the management of pituitary adenomas, with acceptable peri- and postoperative morbidity and mortality. Regardless of the technique used, the presence of large and giant pituitary adenomas with a high Knosp grade represents an enormous challenge for contemporary neurosurgery.

Resumo

Objetivo A cirurgia transesfenoidal é uma técnica segura e eficaz para o tratamento de patologias da base do crânio, como os adenomas hipofisários. O objetivo deste estudo é demonstrar a experiência inicial com a cirurgia endoscópica transesfenoidal no tratamento de pacientes com adenoma hipofisário em hospital terciário, referência em neurocirurgia no Sul do Brasil.

Materiais e Métodos Analisamos retrospectivamente os dados de 60 pacientes com adenoma hipofisário submetidos à cirurgia endoscópica transesfenoidal entre 2012 e 2019. Características demográficas, tipo de tumor, alterações hormonais basais e apresentação clínica foram relatadas, bem como evolução pós-operatória, grau de ressecção tumoral e complicações.

Resultados A proporção homem/mulher foi de 0.53:1, e a idade média da amostra foi de 54 (variação: 26 a 79) anos. Ao todo, 34 pacientes (57%) tinham o subtipo funcional de adenoma, e 26 (43%), o subtipo não funcional de adenoma. Nos grupos não funcional e funcional, o diâmetro médio do tumor foi de 32 mm e 18 mm, e o tempo médio de acompanhamento foi de 27 meses e 32 meses, respectivamente. Em relação aos sintomas visuais, 79% dos pacientes apresentaram melhora após a cirurgia. A remissão hormonal foi alcançada em 71% dos pacientes com adenomas secretores de prolactina, em 85% daqueles com adenomas secretores de hormônio adrenocorticotrófico e em 57% dos pacientes com adenomas secretores de hormônio do crescimento. A ressecção total foi obtida em 50% dos pacientes, mas com taxa significativamente menor em pacientes com tumores com crescimento parasselar (grau elevado na classificação de Knosp). As complicações cirúrgicas mais prevalentes observadas foram fístula liquórica pós-operatória e meningite, em 11% e 6% dos casos, respectivamente.

Conclusão Demostramos que a cirurgia endoscópica transesfenoidal pode produzir bons resultados no manejo de adenomas hipofisários, com aceitável morbimortalidade peri e pós-operatória. Independentemente da técnica utilizada, a presença de adenomas hipofisários grandes e gigantes com grau de Knosp elevado representa um enorme desafio para a neurocirurgia contemporânea.

Palavras-chave
- cirurgia endoscópica
- glândula pituitária
- epidemiologia
- adenoma

Introduction

Transsphenoidal surgery dates back to the beginning of the twentieth century, when pioneering surgeons described the first access to the sella turcica region.[1–5] In 1910, Oskar Hirsch, a Viennese otolaryngologist, described his classic endonasal transseptal transsphenoidal approach;[6,7] in the same year, Albert Halstead described the sublabial access,[5] popularized by Harvey Cushing, who performed more than 2 thousand operations between 1910 and 1925.[7,8]

In Brazil, in 1935, Dr. Correa Meyer and Dr. Eliseu Paglioli described the successful performance of the transsphenoidal access using Hirsch's technique to remove a pituitary tumor.[9] Since the historical technical contributions of Jules Hardy, published in the late 1960s and early 1970s, transsphenoidal surgery has been modernized and became popular as the

best option in the surgical management of intrasellar lesions.[5,10,11]

The advantages over the transcranial access are that it provides excellent visualization of the pituitary gland and neighboring structures, with lower rates of morbidity and mortality.[12] Gerard Guiot is recognized as the first neurosurgeon to use the endoscope in transsphenoidal surgery in 1963.[13]

The experience acquired by ear, nose and throat (ENT) physicians in sinus surgery, associated with that of neurosurgeons using the endoscope in an assisted manner, stimulated an interest in endoscopy that began in the end of the 1980s.[14]

As a result of this collaboration, the use of pure or isolated endoscopy started in the 1990s. In the last 25 years, there has been an exponential growth in its use, and it is currently considered a safe and effective technique to manage different skull base pathologies.[15–30]

Hospital Cristo Redentor (HCR), a public hospital part of Grupo Hospitalar Conceição (GHC), located in the City of Porto Alegre, Southern Brazil, is considered a national reference in neurosurgery. In its facilities, through the effort and integration of the neurosurgery and otorhinolaryngology specialties, endoscopy in transsphenoidal surgery began in 2012.

The objective of the present study is to describe the initial experience with endoscopic transsphenoidal surgery in the treatment of pituitary adenomas at HCR.

Materials and Methods

We conducted a retrospective study to evaluate the first 60 patients with pituitary adenomas submitted to endoscopic transsphenoidal surgery from 2012 to 2019 and treated by the same main team (GP and AM). The study was submitted and approved by the GHC Ethics in Research Committee.

All patients underwent a preoperative evaluation to confirm the diagnosis, which was based on history, clinical examination, laboratory tests, ophthalmological evaluation, and imaging tests.

All patients underwent an evaluation of the pituitary function by the endocrinologist (FA). Imaging studies, such as computed tomography (CT) of the sinuses and magnetic resonance imaging (MRI) of the sella with all sequences, were performed in all cases. The Hammer and Radberg classification[31] was used to assess the extent of pneumatization of the sphenoid sinus in all cases.

The patients were divided into two groups according to the adenoma subtype (non-functioning and functioning), and their respective data were analyzed individually. The sizes of the adenomas were described, and their extensions were classified using Hardy and Vezina[32] and Knosp classifications.[33]

Surgical Technique

The patients were in supine position under general anesthesia and orotracheal intubation, with the back elevated (10°) and the head slightly rotated to the right. Intravenously, a single dose of cefazolin 1 g was administered as a prophylactic antibiotic during the initial phase of anesthesia.

The ENT physician and the neurosurgeon were positioned on the patient's right and left sides respectively. The video tower and rigid endoscopes of 4 mm at 0° and 30° were used, with the recording and storage of images performed routinely.

In the initial phase of the procedure, the nasoseptal flap was harvested. The flap was relocated to the original position at the end of the surgery using suture or biological.

The access to the sellar region was performed following the nasal, sphenoidal, and skull base phases. The use of the two nostrils enabled the surgical teams to work together with the optics and surgical instruments present in the operative field in an integrated manner.

After opening the sella floor and dura mater, tumor removal and subsequent exploration of the sella were performed. The repair was performed sequentially using an abdominal fat graft, the nasoseptal flap, and fibrin glue in patients with the observed opening of the sellar diaphragm and cerebrospinal fluid (CSF) drainage. In these cases, at the end of the surgical procedure, a lumbar drain was maintained for 72 hours.

Considering the high number of cases of postoperative leak observed in the early years, the reconstruction technique was modified by adding bone graft or titanium mesh to reconstruct the sella turcica. (►**Figure 1**). We observed an important decrease in the incidence of postoperative fistula after the routine adoption of this technical modification. The tumor samples collected during the procedures were sent for anatomopathological study and subsequent immunohistochemical analysis.

Postoperative Evaluation

The patients were evaluated postoperatively concerning the neuro-ophthalmological status and endocrinological evaluation. The immunohistochemistry findings were reported, and complications were reviewed and analyzed.

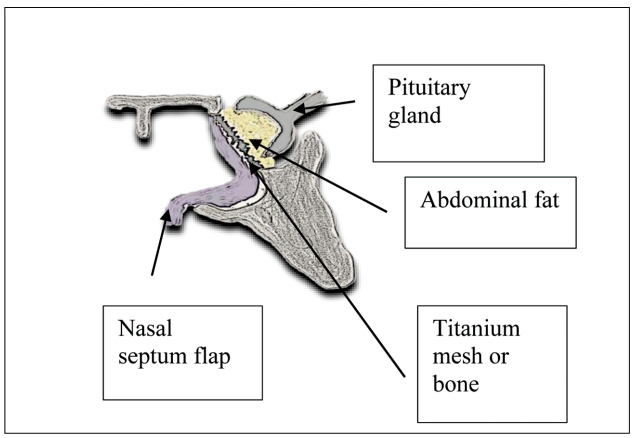


Fig. 1 Schematic drawing of sellar reconstruction using bone or titanium mesh with the application of the nasoseptal graft. Fibrin glue is used to help secure the flap.

During the follow-up, the patients underwent MRI between 3 months and 1 year after the surgery. According to the last control performed, tumor removal was classified as gross total resection or subtotal/partial resection. Patients with functioning tumors were followed up by the endocrinology team using laboratory criteria and clinical symptoms to define the criteria for disease remission.

Results

Overall, we operated 60 patients with pituitary adenomas, 21 male (35%) and 39 female subjects (65%), with a mean age of 54 years: 34 cases were classified as non-functioning adenoma and 26, as functioning.

Hormone changes, with hyperfunction or hypofunction, were often found as the clinical presentation, as well as visual symptoms. Regarding the group with functioning tumors, 11 patients presented acromegaly, 7 subjects had macroprolactinomas, 7 presented Cushing syndrome, and 1 patient had hyperthyroidism/acromegaly syndrome.

Hypogonadism, hypothyroidism, and hypocortisolism were found in 26%, 23%, and 5% of the cases respectively. Panhypopituitarism was found in 5% of the patients, and 78% had preoperative vision disorder manifested by changes in the visual field or loss of visual acuity.

Symptoms such as headache were observed in 18% of the cases, while mental confusion, seizure, and hemiparesthesia were seen in 3%. A total of 3 patients (5%) had undergone previous surgical treatment; all of them underwent transsphenoidal microsurgery in other institutions.

Demographic characteristics, type of tumor, baseline hormonal changes, clinical presentation, and previous surgery history are summarized in ►**Table 1**.

Suprasellar extension greater than 20 mm was observed in 20 patients (59%) in the non-functioning group and only in 3 patients (12%) in the functioning group. In the functioning group, 18 patients (69%) presented suprasellar extension measuring between 0 mm and 10 mm.

Regarding the Knosp classification, in the non-functioning group, 21 patients (65%) were categorized as grades 0 to 2, and 13 patients (35%), as grades 3 to 4. In the functioning tumor group, 21 patients (81%) were classified as grades 0 to 2, and 5 (19%), as grades 3 to 4. The suprasellar extension and degree of cavernous sinus invasion (Knosp scale) of both groups are detailed in ►**Table 2** and ►**Figures 2, 3, 4** and **5**.

According to the Hammer and Radberg classification, 6 patients (10%) had a sinus of the presellar type, equally distributed between the two groups of patients. Most patients had the sellar type, and no cases of sphenoidal sinus of the conchal type were observed.

(►**Table 3**)

Surgical Results

Regarding the immunohistochemistry results, in the group of non-functioning adenomas, 16 patients (47%) presented "null cell". In the functioning group, the results showed gonadotropin, adrenocorticotropic hormone (ACTH), and prolactin in 41%, 6%, and 3% of the cases respectively.

Table 1 Baseline characteristics of the patients

Characteristics	N	Percentage
Patients	60	100%
Male	21	35%
Female	39	65%
Mean age	54 years old	
Non-functioning adenomas	34	57%
Functioning adenomas	26	43%
Hyperprolactinemia	7	12%
Growth hormone-secreting adenoma	11	18%
Adrenocorticotropic hormone -secreting adenoma	7	12%
Thyroid-stimulating hormone/ growth hormone-secreting adenoma	1	2%
Hypogonadism	16	26%
Hypothyroidism	14	23%
Hypocortisolism	3	5%
Panhypopituitarism	3	5%
Visual field deficit	26	43%
Abnormal visual acuity	21	35%
Headache	11	18%
Mental confusion	2	3%
Hemiparesthesia	2	3%
Seizure	2	3%
Previous surgery	3	5%

Still according to the immunohistochemistry results, in the functioning group, there were 7 patients (27%) with tumors that secreted growth hormone (GH), 7 (27%) patients with prolactin-secreting tumors, 4 patients (15%) with ACTH-secreting tumors, and only 1 patient (4%) with a tumor that secreted thyroid-stimulating hormone (TSH) (►**Table 4**).

Regarding the visual symptoms 79% of the patients experienced improvement after surgery, while 15% remained stable, and 6% presented worsening of the deficit in the postoperative period.

Hormonal disfunction was found in 55% of the patients, a rate similar to the preoperative rate. None of the patients progressed to panhypopituitarism, and there were no cases of improvement in the pituitary function during the postoperative follow-up period. A total of 54 patients underwent postoperative MRI between 3 months and 1 year, there were 5 cases of loss to outpatient follow-up, and 1 patient died in the first month after surgery.

Overall, GTR was possible in 27 cases (50%). In the non-functioning group, it was achieved in 12 patients (37%), and, in the remaining cases, the resection was subtotal or partial.

Table 2 Size, suprasellar extension and degree of cavernous sinus invasion (Knosp scale) of the tumors

Radiological characteristics	Adenoma	Non-functioning – n (%)	Functioning – n (%)
Number of cases	60	34 (56.6)	26 (43.4)
Size (mm)	0-10	0 (0.0)	3 (11)
	10-20	2 (6)	15 (58)
	20-30	15 (44)	5 (19)
	30-40	11 (32)	2 (8)
	40-50	6 (18)	1 (4)
Median (mm)		32	18
Suprasellar extension	0-10	2 (6)	18 (69)
	10-20	12 (35)	5 (19)
	20-30	17 (50.0)	2 (8)
	> 30	3 (9)	1 (4)
Grade on the Knosp classification	0	5 (15)	15 (58)
	1	5 (15)	5 (19)
	2	11 (35)	1 (4)
	3	7 (19)	3 (11)
	4	6 (16)	2 (8)

The rate of GTR showed a difference when comparing the Knosp 0-2 and Knosp 3-4 patients: it was significantly lower in tumors with a high grade on the Knosp classification ($p < 0.05$).

Complete resection was achieved in 69% of the Knosp 0-2 patients and all Knosp 3-4 subjects underwent subtotal or partial resection. In total, 7 patients (13%) in whom only partial resection was achieved were referred for a new surgery; 3 of them underwent a new endoscopic endonasal procedure, and 4 were referred for craniotomy. After the second procedure, GTR was achieved in 3 (43%) patients, and the 4 (67%) remaining subjects with residual tumors were referred for radiotherapy. The 13 (40%) patients who remained with subtotal resection showed no progression of the symptoms during the follow-up period and were kept under outpatient observation.

Details of the results found for each functioning tumor subtype are described as follows.

Growth Hormone-Secreting Adenomas

Growth hormone-secreting adenoma was the most common hormone-secreting adenoma found in our series: 4 out of 11 patients were excluded due to loss to follow-up; all the remaining 7 patients had macroadenomas, and 1 of them had a cystic characteristic.

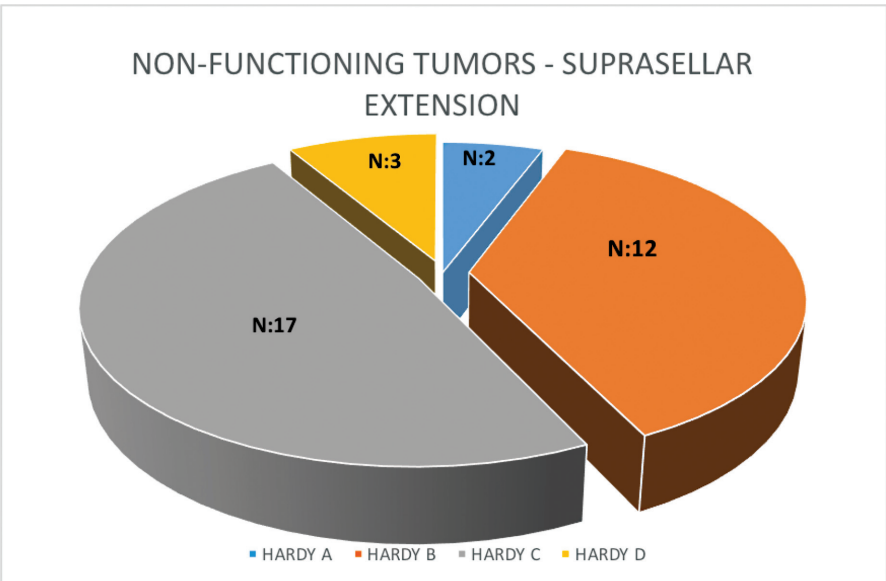


Fig. 2 The graph shows the number of cases of non-functioning tumors classified by the Hardy grade. 17 patients had Hardy grade A, 12 Hardy grade B, 2 Hardy grade C and 3 Hardy grade D.

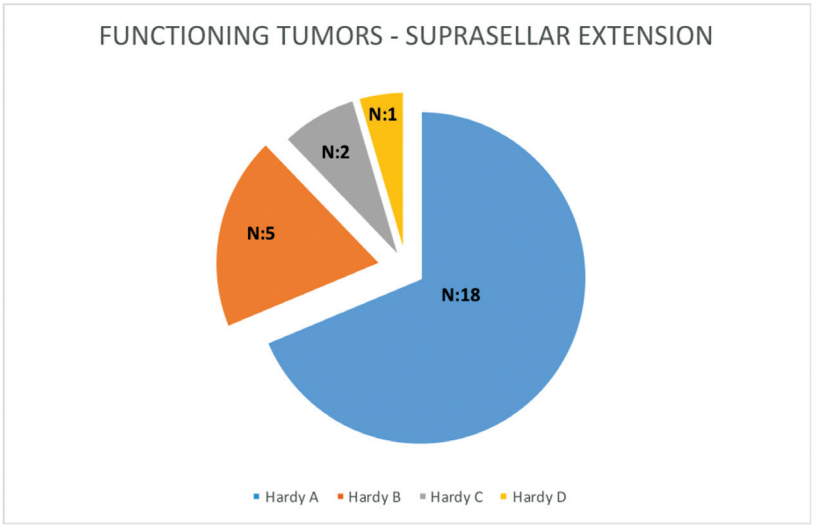


Fig. 3 The graph shows the number of cases of functioning tumors classified by the Hardy grade. 18 patients had Hardy grade A, 5 Hardy grade B, 2 Hardy grade C and 1 Hardy grade D.

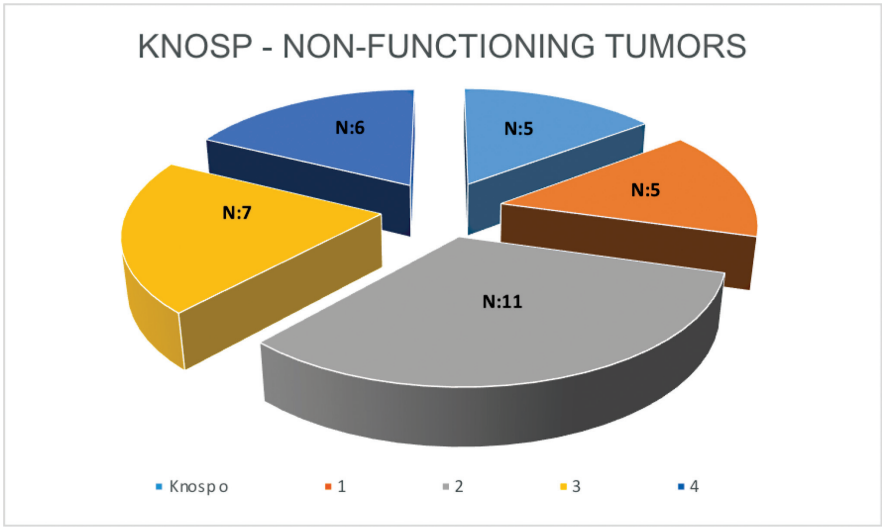


Fig. 4 The graph shows the number of cases of non-functioning tumors classified by the Knosp grade. 5 patients had Knosp grade 0, 5 Knosp grade 1, 11 Knosp grade 2, 7 Knosp grade 7 and 6 Knosp grade 4.

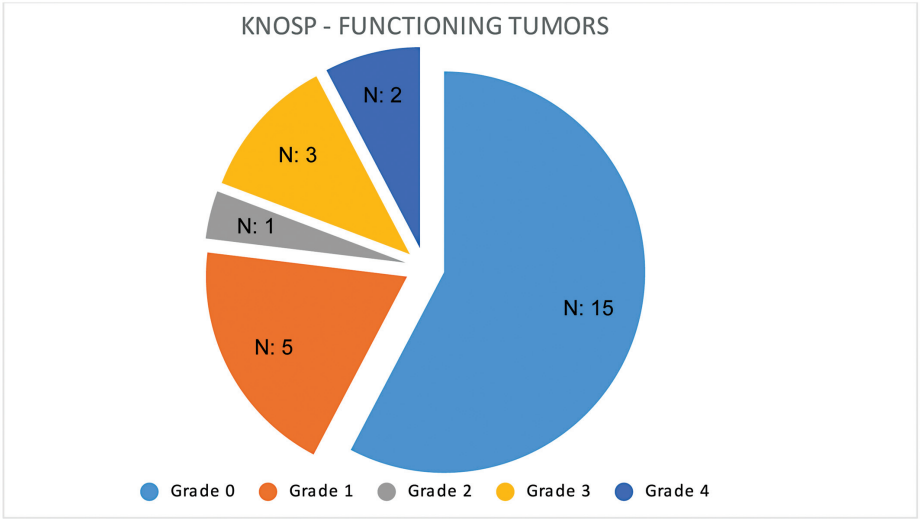


Fig. 5 The graph shows the number of cases of functioning tumors classified by the Knosp grade. 15 patients had Knosp grade 0, 5 Knosp grade 1, 1 Knosp grade 2, 3 Knosp grade 3 and 2 Knosp grade 4.

Table 3 Type of sphenoid sinus for functioning and non-functioning adenoma groups. The sellar type sinus was the most frequent in both groups

Sphenoid sinus type	Non-Functioning adenomas – n (%)	Functioning adenomas – n (%)
Sellar	31 (91)	23 (89)
Presellar	3 (9)	3 (11)
	TOTAL: 34 (100)	TOTAL: 26 (100)

Table 5 Number of complications identified in the sample. The most common were intraoperative CSF leak and transient diabetes insipidus

Complications	n (%)
Intraoperative cerebrospinal fluid leak	13 (24)
Postoperative cerebrospinal fluid leak	6 (11)
Meningitis	4 (7.4)
Intrasellar hematoma	2 (3.6)
Empty sella with downward displacement of suprasellar visual system	1 (1.8)
Transient diabetes insipidus	9 (16.6)
Death	1 (1.8)

In 4 patients (57%), hormonal control was achieved in the postoperative period. The 3 patients without hormonal control after the surgery showed a good clinical response to pharmacological treatment during the follow-up.

Prolactinomas

Of the 7 patients with prolactinomas selected for surgery, 6 had macroadenomas with cystic and/or hemorrhagic characteristics. One patient had a macroadenoma with a high Knosp grade presented with no hormonal control using dopaminergic agonists. We achieved overall hormonal control after surgery in 5 patients (71%).

Table 4 Summary of the immunohistochemistry findings

Immunohistochemistry	Non-functioning tumors – n (%)	Functioning tumors – n (%)
Null cell	16 (47)	5 (19)
Adrenocorticotropic hormone -secreting adenoma	2 (6)	4 (15)
Gonadotropin-secreting adenoma	14 (41)	1 (4.0)
Prolactin-secreting adenoma	1 (3)	7 (27)
Thyroid-stimulating hormone-secreting adenoma	0 (0)	1 (4.0)
Growth hormone-secreting adenoma	0 (0.0)	7 (27.0)
Multihormonal production	0 (0.0)	1 (4)
Total patients	34 (100)	26 (100)

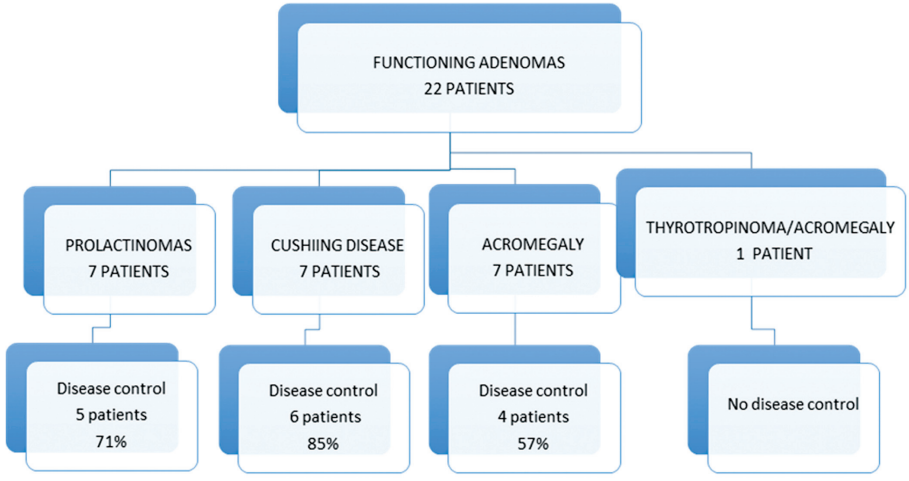
ACTH-Secreting Adenoma

A total of 6 patients had macroadenomas with sizes ranging from 10 mm to 20 mm, and only 1 patient had a microadenoma with a size of 6 mm. No tumor had cystic characteristics, and there was hormonal control after surgery in 6 cases (85%) during the follow-up.

TSH/GH-secreting Adenoma

In the present series, we found one patient with a macroadenoma with lateral extension (Knosp 4) and a plurihormonal profile (GH- and TSH-secreting). After the surgery, the TSH and GH values remained high, although lower than in the preoperative period. A control MRI showed subtotal resection (presence of residual tumor within the cavernous sinus). After introducing the drug treatment, reduction and control of the hormonal levels maintained during the follow-up period were achieved. The mean follow-up time was of 27 months and 32 months in the non-functioning and functioning adenoma groups respectively.

Details of the surgical results for each subgroup are shown in the following organizational chart:



Complications

Intraoperative CSF leak is the most frequent complication, and it was found in 13 patients (24%), followed by postoperative CSF leak in 6 patients (11%).

There were 4 patients (7.4%) with meningitis; 3 of them showed good evolution, but 1 developed severe meningitis and ventriculitis complications and died after a long period of hospitalization. One patient had epistaxis on the first day after surgery and needed to be reoperated.

According to the postoperative tomography, 2 patients (3.6%) with large tumors developed intrasellar hematoma. The management was conservative, given the stability of the visual symptoms. One case of a male patient with late visual deterioration (one year after surgery) was associated with chiasma prolapse in the empty sella. He underwent a transcranial approach for chiasmapexy, and evolved with the improvement in the visual deficit.

Transient diabetes insipidus (DI) was observed in 9 patients (16.6%), but there were no cases of postoperative permanent DI. All of them were managed in the intensive care unit and showed good response to the clinical interventions.

There was a death related to CSF fistula and central nervous system (CSN) infection that occurred within 30 days of the surgery. The complications have been summarized in ►**Table 5**.

Discussion

Transsphenoidal surgery is considered an excellent alternative to craniotomy in the management of most pituitary adenomas.[34]

Throughout the twentieth century, the technique underwent improvements and modifications,[35] and the use of endoscopy in transsphenoidal surgery is considered a recent breakthrough.[36]

According to Yu et al.,[37] endoscopic endonasal transsphenoidal surgery in the treatment of pituitary adenomas presents results that are similar or better than those of traditional microscopy in terms of mass removal, improvement in visual symptoms, and preservation of endocrine function.

Regarding nasal morbidity and quality of life, it can be said that the endoscopic technique is less morbid because it does not use a sublabial incision or nasal plug, besides producing lower levels of mucosal detachment.[38,39]

The technical advantages of endoscopic endonasal transsphenoidal surgery are related to an increase in the working angle, enabling a close and panoramic view of the anatomical structures.[27,40,41]

In the present study, we performed the isolated or pure endoscopic technique, in which only the endoscope is used in all stages of the procedure, as described by several authors in the 1990s.[15–18]

In the present series, most of the tumors were macroadenomas. Analyzing the groups of patients with non-functioning and functioning adenomas, we observed that the mean sizes of the tumors was of 32 mm and 18 mm respectively, which are larger than the sizes reported in some of the previously described series.[42,43]

Delay in diagnosis due to the difficulty on the part of the patients to access our health system could explain this finding.

Non-Functioning Tumors

The main objectives of the surgical treatment of non-functioning adenomas are to preserve the neighboring neural structures, to prevent functional worsening of the pituitary and visual function, and to revert any functional impact on the surrounding neural structures.[44] Although the improvement in pituitary function in the postoperative period has been reported to range from 16% to 48% of the cases,[45] no improvements were reported in previous series.[46,47] In the present study, pituitary function remained unchanged, with no improvement or worsening observed in any patient.

According to Wichers-Rother et al.,[47] the objective of transsphenoidal surgery is to improve visual field defects rather than to improve the pituitary function. Regarding vision, 79% of our patients showed visual improvement in the postoperative period, a rate similar to that of previous reports.[44,45,48] In the present series, the rate of 37% of GTR in the non-functioning group is lower than the one reported in previous endoscopic series.[49–55] This result is related to the learning curve of the endoscopic technique[56] associated with the findings of large tumors with frequent lateral extension. Patients with high Knosp grades are more likely to present tumor invasion of the parasellar region, which decreases the chance of GTR.[57] Accordingly, we found a statistically significant difference in GTR when comparing patients with Knosp grades 0 to 2 and 3 to 4.

Tumors with Knosp grade 3 or 4 have a greater degree of cavernous sinus invasion and were predictors of greater difficulty in achieving a GTR.

In the present study, the approaches were restricted to the sellar region, which certainly limited the possibility of achieving GTR in tumors of larger size and volume.

Biological factors inherent to the tumor are important in relapse, so not all residual lesions will present a regrowth over time.[46,58] In agreement with this, 13 patients (40%) in whom residual lesions were observed on the postoperative MRI in the present study did not present any changes during the follow-up.

As the postoperative recurrence rate for non-functioning tumors peaks between 1 and 5 years and only reduces after 10 years, it is essential to maintain the follow-up of these patients for longer periods.[59]

Functioning Tumors

Tumors that secrete GH and prolactin are the most common type of functioning pituitary adenomas.[49] In the present series, we found more GH-secreting adenomas (37%) and an equal number of ACTH- and prolactin-secreting adenomas (29%).

Regarding the subjects with GH-secreting tumors, we obtained control of hormonal levels in 4 patients (57%), a rate similar to the 56.4% mean historical control rate for first-time surgery.[60]

According to Nomikos et al.,[61] the remission rate in patients undergoing transsphenoidal surgery tended to decrease in macroadenomas, being of 33.3% for suprasellar tumors with visual impairment and of 44.5% for suprasellar tumors without impairment. In our case series, patients with acromegaly had large lesions, more than 1 cm in diameter, and we achieved a remission rate in 57% of cases.

Managing patients with acromegaly without control of hormonal levels after the first operation is a matter of discussion.[61] Three patients in whom control was not achieved after surgery were referred for drug treatment and showed good clinical response during the follow-up.

Regarding prolactinomas, although we found large tumors (the largest measuring 45 mm), most of them had cystic or hemorrhagic characteristics, increasing the chance of achieving GTR. Our resection rate of 71% for prolactin-secreting macroadenomas is similar to rates in previously described series.[53,62,63]

The surgical treatment of prolactinomas is indicated in patients who have tolerance or resistance to the use of dopaminergic agonists or who have tumors larger than 20 mm with an associated visual deficit.[53] In some countries, the cost of the drug treatment is also considered in this decision.[49] Therefore, there is some controversy about the best management. According to Donoho and Laws (ref [64]), patients with prolactinomas in the subacute evolution and mild early visual changes can be controlled with medication.

There is some controversy about the best management. According to Donoho and Laws,[64] patients with prolactinomas in subacute evolution and mild early visual changes could be managed with medications.

On the other hand, Akinduro et al.[65] report that, given the significant reduction in the largest tumor volume and prolactin levels occurring within six months after starting the treatment, surgery would play an important role in patients with a large tumor and acute visual deterioration.

We agree that patients with prolactin-secreting macroadenomas with cystic/hemorrhagic characteristics, suprasellar growth, and visual loss may actually benefit from the endoscopic endonasal transsphenoidal surgery.

Our disease control rate of 85% for Cushing disease is superior to that of a previous endoscopic series,[66] considering that 6 of the 7 operated patients had macroadenomas.

As previously described, the recurrence rate for Cushing disease can vary from 10% to 30% up to 10 years after surgery,[67,68] with 50% of recurrences occurring during the first 50 months after surgery.[69] Considering that our follow-up was of 32 months, there is a need for longer follow-up periods to confirm the remission rate.

Tumors that secrete TSH (thyrotropinomas) are very rare pituitary tumors, corresponding to 1% to 5% of the cases.[70–72] They often concomitantly secrete other pituitary hormones, such as prolactin, gonadotropins, and GH, which is the most frequently co-secreted hormone.[71]

These tumors show an aggressive growth pattern and are harder to control only with surgery compared with other types of adenomas. Therefore, radiotherapy and drug treatment should be considered in the case of surgical failure.[72]

In the present series, one patient had a macroadenoma that simultaneously secreted TSH and GH. This patient underwent subtotal resection and achieved hormonal control during the follow-up after using long-acting somatostatin analogs.

Complications

The occurrence of intraoperative and postoperative CSF leaks in endoscopic surgery of pituitary adenomas varies from 16% b to 26% and from 1.3% to 10.3% respectively.[73,74]

According to Lobatto et al.,[75] the following preoperative risk factors are associated with a potential higher risk of CSF leak: adenomas with intraventricular extension, age under 65 years, being female, peptic ulcer disease, and high body mass index (BMI). Boling et al.[76] describe intraventricular extension as the main risk factor associated with the occurrence of postoperative fistula, and they suggest aggressive treatment of the intraoperative fistula in these cases.[76]

The learning curve is also considered an important factor associated with the risk of CSF leak and most of the complications described.[73] In the present study, our CSF leak rate of 11% is strongly associated with the learning curve.

In endoscopic pituitary surgery, the incidence of intracranial infection ranges from 0 to 9.8%.[75] Longer operative time, diabetes mellitus, and intraoperative CSF leak are the main factors associated with its occurrence.[77] In the present study, the rate of CNS infection was of 7.4%, which falls within this range. All cases were associated with the occurrence of intraoperative CSF leak.

The occurrence of intratumoral bleeding of large and giant adenomas in the postoperative period has been reported to range from 2.1% to 3.7%.[78–80] Considering the high risk of visual deterioration, emergency craniotomy should always be considered in the management of this complication.[81] In the present study, the rate of intratumoral bleeding of 3.6% is similar to the rates reported in previous series. The patients in the present study who suffered from this complication did not show any visual deterioration, and they were not referred to emergency craniotomy.

The association of an empty sella with visual impairment was described almost 50 years ago.[82] Such a condition is associated with delayed visual deterioration after pituitary surgery.[83] The pathophysiology would be the presence of scar tissue related to the secondary empty sella, causing retraction and lower displacement of the sellar diaphragm and the optic apparatus. The repair of such a condition, known as chiasmapexy, can be performed by the transcranial or transsphenoidal routes.[84]

In the present series the only patient with chiasmapexy needed a transcranial repair in which retraction of the optic apparatus and its lower displacement along with the sellar diaphragm were observed. Release of fibrosis and scar tissue adhered to the optic nerves was achieved, improving visual acuity in the postoperative period.

Although it is a rare condition, the pituitary surgeon must watch out for patients with visual deterioration in the late postoperative period associated with the presence of an empty sella.

The prevalence of temporary and permanent DI is of 9.1 and 2.3% respectively, which is significantly lower when compared to microsurgery.[85] According to Kim et al.,[52] invasive tumors, previous surgery, and radiotherapy can increase its prevalence. In the present series, 9 patients (16.6%) developed transient DI, and none developed permanent DI.

The overall mortality rate in the present series was 1.8% (1 patient), which is higher than the mean rate of 0.5% reported in the literature.[76] The case was directly related to the surgical procedure (CSF leak/meningitis).

There certainly is a learning curve regarding the use of the endoscopic technique. As the experience increases, the incidence of complications as a whole will obviously decrease. This current study describes a small sample submitted to the initial experience with endoscopy in transsphenoidal surgery.

Conclusion

The current study describes a small sample submitted to the initial experience with endoscopy in transsphenoidal surgery in a public tertiary hospital, a reference in neurosurgery in Southern Brazil. We were able to show that the technique can yield good results in the management of pituitary tumors, with acceptable peri- and postoperative morbidity and mortality. Regardless of the technique currently used, the presence of large and giant pituitary adenomas with high Knosp grades represents a great challenge for contemporary neurosurgery.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Liu JK, Das K, Weiss MH, Laws ER Jr, Couldwell WT. The history and evolution of transsphenoidal surgery. J Neurosurg 2001;95(06): 1083–1096

2 Prevedello DM, Doglietto F, Jane JAJ Jr, Jagannathan J, Han J, Laws ERJ Jr. History of endoscopic skull base surgery: its evolution and current reality. J Neurosurg 2007;107(01):206–213

3 Grosvenor AE, Laws ER. The evolution of extracranial approaches to the pituitary and anterior skull base. Pituitary 2008;11(04): 337–345

4 Artico M, Pastore FS, Fraioli B, Giuffrè R The contribution of Davide Giordano (1864-1954) to pituitary surgery: the transglabellar-nasal approach. Neurosurgery 1998;42(04):909–911, discussion 911–912. Doi: 10.1097/00006123-199804000-00121

5 Kanter AS, Dumont AS, Asthagiri AR, Oskouian RJ, Jane JA Jr, Laws ER Jr. The transsphenoidal approach. A historical perspective. Neurosurg Focus 2005;18(04):e6

6 Liu JK, Cohen-Gadol AA, Laws ERJ Jr, Cole CD, Kan P, Couldwell WT. Harvey Cushing and Oskar Hirsch: early forefathers of modern transsphenoidal surgery. J Neurosurg 2005;103(06):1096–1104

7 Lanzino G, Laws ERJ Jr. Pioneers in the development of transsphenoidal surgery: Theodor Kocher, Oskar Hirsch, and Norman Dott. J Neurosurg 2001;95(06):1097–1103

8 Rosegay H. Cushing's legacy to transsphenoidal surgery. J Neurosurg 1981;54(04):448–454

9 Meyer C, Ritter F. Tumor de Hipófise: Operação de Hirsch-Segura. - Estudo neuro-clínico e oftalmologico. Rev dos Cursos. Fac Med. 1935;21(21):1–23

10 Hardy J. Transphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg 1969;16:185–217

11 Hardy J. Transsphenoidal hypophysectomy. J Neurosurg 1971;34 (04):582–594

12 Cavallo LM, Messina A, Cappabianca P, et al. Endoscopic endonasal surgery of the midline skull base: anatomical study and clinical considerations. Neurosurg Focus 2005;19(01):E2

13 Castelnuovo P, Dallan I, Battaglia P, Bignami M. Endoscopic endonasal skull base surgery: past, present and future. Eur Arch Otorhinolaryngol 2010;267(05):649–663

14 Doglietto F, Prevedello DM, Jane JAJ Jr, Han J, Laws ERJ Jr. Brief history of endoscopic transsphenoidal surgery–from Philipp Bozzini to the First World Congress of Endoscopic Skull Base Surgery. Neurosurg Focus 2005;19(06):E3

15 Jankowski R, Auque J, Simon C, Marchal JC, Hepner H, Wayoff M. Endoscopic pituitary tumor surgery. Laryngoscope 1992;102 (02):198–202

16 Sethi DS, Pillay PK. Endoscopic management of lesions of the sella turcica. J Laryngol Otol 1995;109(10):956–962

17 Jho H-D, Carrau RL. Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. J Neurosurg 1997;87(01):44–51https://thejns.org/view/journals/j-neurosurg/87/1/article-p44.xml

18 Cappabianca P, Alfieri A, de Divitiis E. Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPS). Minim Invasive Neurosurg 1998; 41(02):66–7310.1055/s-2008-1052019

19 Alfieri A, Jho H-D, Tschabitscher M. Endoscopic endonasal approach to the ventral cranio-cervical junction: anatomical study. Acta Neurochir (Wien) 2002;144(03):219–225, discussion 225http://www.ncbi.nlm.nih.gov/pubmed/11956934

20 Cappabianca P, Frank G, Pasquini E, de Divitiis O, Calbucci F. Extended endoscopic endonasal transsphenoidal approaches to the suprasellar region, planum sphenoidale and clivus. In: de Divitiis E, Cappabianca P, eds. Endoscopic Endonasal Transsphenoidal Surgery [Internet]. Vienna: Springer Vienna; 2003: 176–187. Available from: https://doi.org/10.1007/978-3-7091-6084-8_11

21 Solari D, Morace R, Cavallo LM, et al. The endoscopic endonasal approach for the management of craniopharyngiomas. J Neurosurg Sci 2016;60(04):454–462

22 Linsler S, Oertel J. Endoscopic Endonasal Transclival Resection of a Brainstem Cavernoma: A Detailed Account of Our Technique and Comparison with the Literature. World Neurosurg 2015;84(06): 2064–2071

23 Kassam AB, Gardner P, Snyderman C, Mintz A, Carrau R. Expanded endonasal approach: fully endoscopic, completely transnasal approach to the middle third of the clivus, petrous bone, middle cranial fossa, and infratemporal fossa. Neurosurg Focus 2005;19 (01):E6

24 Frank G, Pasquini E, Doglietto F, et al. The endoscopic extended transsphenoidal approach for craniopharyngiomas. Neurosurgery 2006;59(1, Suppl 1)ONS75–ONS83, discussion ONS75–ONS83

25 Snyderman C, Kassam A, Carrau R, Mintz A. Endoscopic approaches to the petrous apex. Oper Tech Otolaryngol Neck Surg. 2006;17:168–173

26 Fernandez-Miranda JC, Gardner PA, Prevedello DM, Kassam AB. Expanded endonasal approach for olfactory groove meningioma. Acta Neurochir (Wien) 2009;151(03):287–288, author reply 289–290

27 Dehdashti AR, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for anterior cranial base and

suprasellar lesions: indications and limitations. Neurosurgery 2009;64(04):677–687, discussion 687–689
28 Shin M, Kondo K, Saito N. Current Status of Endoscopic Endonasal Surgery for Skull Base Meningiomas: Review of the Literature. Neurol Med Chir (Tokyo) 2015;55(09):735–743https://pubmed.ncbi.nlm.nih.gov/26345667
29 Mangussi-Gomes J, Beer-Furlan A, Balsalobre L, Vellutini EAS, Stamm AC. Endoscopic Endonasal Management of Skull Base Chordomas: Surgical Technique, Nuances, and Pitfalls. Otolaryngol Clin North Am 2016;49(01):167–182
30 Zoli M, Milanese L, Bonfatti R, et al. Clival chordomas: considerations after 16 years of endoscopic endonasal surgery. J Neurosurg 2018;128(02):329–338
31 Hammer G, Rådberg C. The sphenoidal sinus. An anatomical and roentgenologic study with reference to transsphenoid hypophysectomy. Acta Radiol 1961;56(06):401–422https://journals.sagepub.com/doi/abs/10.1177/028418516105600601
32 Hardy J, Vezina JL. Transsphenoidal neurosurgery of intracranial neoplasm. Adv Neurol 1976;15:261–273
33 Knosp E, Steiner E, Kitz K, Matula C. Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery 1993;33(04):610–617, discussion 617–618
34 Li H-Y, Feng C-Y, Zhang C, et al. Microscopic surgery for pituitary adenomas to preserve the pituitary gland and stalk. Exp Ther Med 2017;13(03):1011–1016
35 Gandhi CD, Christiano LD, Eloy JA, Prestigiacomo CJ, Post KD. The historical evolution of transsphenoidal surgery: facilitation by technological advances. Neurosurg Focus 2009;27(03):E8
36 Theodros D, Patel M, Ruzevick J, Lim M, Bettegowda C. Pituitary adenomas: historical perspective, surgical management and future directions. CNS Oncol 2015;4(06):411–429
37 Yu S-Y, Du Q, Yao S-Y, et al. Outcomes of endoscopic and microscopic transsphenoidal surgery on non-functioning pituitary adenomas: a systematic review and meta-analysis. J Cell Mol Med 2018;22(03):2023–2027https://pubmed.ncbi.nlm.nih.gov/29314715
38 White DR, Sonnenburg RE, Ewend MG, Senior BA. Safety of minimally invasive pituitary surgery (MIPS) compared with a traditional approach. Laryngoscope 2004;114(11):1945–1948
39 Nishioka H. Recent Evolution of Endoscopic Endonasal Surgery for Treatment of Pituitary Adenomas. Neurol Med Chir (Tokyo) 2017;57(04):151–158https://pubmed.ncbi.nlm.nih.gov/28239067
40 O'Malley BWJ Jr, Grady MS, Gabel BC, et al. Comparison of endoscopic and microscopic removal of pituitary adenomas: single-surgeon experience and the learning curve. Neurosurg Focus 2008;25(06):E10
41 Cappabianca P, Cavallo LM, Solari D, Stagno V, Esposito F, de Angelis M. Endoscopic endonasal surgery for pituitary adenomas. World Neurosurg 2014;82(06):S3–S11
42 Tabaee A, Anand VK, Barrón Y, et al. Predictors of short-term outcomes following endoscopic pituitary surgery. Clin Neurol Neurosurg 2009;111(02):119–122
43 Jain AK, Gupta AK, Pathak A, Bhansali A, Bapuraj JR. Endonasal transsphenoidal pituitary surgery: is tumor volume a key factor in determining outcome? Am J Otolaryngol 2008;29(01):48–50
44 Esposito D, Olsson DS, Ragnarsson O, Buchfelder M, Skoglund T, Johannsson G. Non-functioning pituitary adenomas: indications for pituitary surgery and post-surgical management. Pituitary 2019;22(04):422–434
45 Penn DL, Burke WT, Laws ER. Management of non-functioning pituitary adenomas: surgery. Pituitary 2018;21(02):145–153
46 Dekkers OM, Pereira AM, Roelfsema F, et al. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 2006;91(05):1796–1801
47 Wichers-Rother M, Hoven S, Kristof RA, Bliesener N, Stoffel-Wagner B. Non-functioning pituitary adenomas: endocrinological and clinical outcome after transsphenoidal and transcranial surgery. Exp Clin Endocrinol Diabetes 2004;112(06):323–327
48 Murad MH, Fernández-Balsells MM, Barwise A, et al. Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2010;73(06):777–791
49 Wang F, Zhou T, Wei S, et al. Endoscopic endonasal transsphenoidal surgery of 1,166 pituitary adenomas. Surg Endosc 2015;29(06):1270–1280
50 Gondim JA, Schops M, de Almeida JPC, et al. Endoscopic endonasal transsphenoidal surgery: surgical results of 228 pituitary adenomas treated in a pituitary center. Pituitary 2010;13(01):68–77
51 Cappabianca P, Cavallo LM, de Divitiis E. Endoscopic endonasal transsphenoidal surgery. Neurosurgery 2004;55(04):933–940, discussion 940–941
52 Kim JH, Lee JH, Lee JH, Hong AR, Kim YJ, Kim YH. Endoscopic Transsphenoidal Surgery Outcomes in 331 Nonfunctioning Pituitary Adenoma Cases After a Single Surgeon Learning Curve. World Neurosurg 2018;109:e409–e416
53 Torales J, Halperin I, Hanzu F, et al. Endoscopic endonasal surgery for pituitary tumors. Results in a series of 121 patients operated at the same center and by the same neurosurgeon. Endocrinol Nutr 2014;61(08):410–416
54 Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery 2008;62(05):1006–1015, discussion 1015–1017
55 Bokhari AR, Davies MA, Diamond T. Endoscopic transsphenoidal pituitary surgery: a single surgeon experience and the learning curve. Br J Neurosurg 2013;27(01):44–49
56 Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurgery 1997;40(02):225–236, discussion 236–237
57 Micko ASG, Wöhrer A, Wolfsberger S, Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. J Neurosurg 2015;122(04):803–811
58 Maletkovic J, Dabbagh A, Zhang D, et al. Residual Tumor Confers a 10-Fold Increased Risk of Regrowth in Clinically Nonfunctioning Pituitary Tumors. J Endocr Soc 2019;3(10):1931–1941
59 Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis. Pituitary 2012;15(01):71–83https://pubmed.ncbi.nlm.nih.gov/21918830
60 Almeida JP, Ruiz-Treviño AS, Liang B, et al. Reoperation for growth hormone-secreting pituitary adenomas: report on an endonasal endoscopic series with a systematic review and meta-analysis of the literature. J Neurosurg 2018;129(02):404–416
61 Nomikos P, Buchfelder M, Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. Eur J Endocrinol 2005;152(03):379–387
62 Han Y-L, Chen D-M, Zhang C, Pan M, Yang X-P, Wu Y-G. Retrospective analysis of 52 patients with prolactinomas following endoscopic endonasal transsphenoidal surgery. Medicine (Baltimore) 2018;97(45):e13198–e13198https://pubmed.ncbi.nlm.nih.gov/30407358
63 Zielinski G, Ozdarski M, Maksymowicz M, Szamotulska K, Witek P. Prolactinomas: Prognostic Factors of Early Remission After Transsphenoidal Surgery. Front Endocrinol (Lausanne) 2020;11:439
64 Donoho DA, Laws ER Jr. The Role of Surgery in the Management of Prolactinomas. Neurosurg Clin N Am 2019;30(04):509–514. Doi: 10.1016/j.nec.2019.05.010
65 Akinduro OO, Lu VM, Izzo A, et al. Radiographic and Hormonal Regression in Prolactinomas: An Analysis of Treatment Failure. World Neurosurg 2019;129:e686–e694

66 Ferriere A, Tabarin A. Cushing's syndrome: Treatment and new therapeutic approaches. Best Pract Res Clin Endocrinol Metab 2020;34(02):101381
67 Patil CG, Prevedello DM, Lad SP, et al. Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. J Clin Endocrinol Metab 2008;93(02):358–362. Doi: 10.1210/jc.2007-2013
68 Pivonello R, De Leo M, Cozzolino A, Colao A. The Treatment of Cushing's Disease. Endocr Rev 2015;36(04):385–486https://pubmed.ncbi.nlm.nih.gov/26067718
69 Braun LT, Rubinstein G, Zopp S, et al. Recurrence after pituitary surgery in adult Cushing's disease: a systematic review on diagnosis and treatment. Endocrine 2020;70(02):218–231. Doi: 10.1007/s12020-020-02432-z
70 Johnston PC, Hamrahian AH, Prayson RA, Kennedy L, Weil RJ. Thyrotoxicosis with absence of clinical features of acromegaly in a TSH- and GH-secreting, invasive pituitary macroadenoma. Endocrinol Diabetes Metab Case Rep 2015;2015:140070
71 Lee EY, Ku CR, Kim HM, et al. A Case of Pituitary Adenoma with Simultaneous Secretion of TSH and GH. Endocrinol Metab (Seoul) 2011;26(02):160–165. Doi: 10.3803/EnM.2011.26.2.160
72 Berker D, Isik S, Aydin Y, et al. Thyrotropin secreting pituitary adenoma accompanying a silent somatotropinoma. Turk Neurosurg 2011;21(03):403–407
73 Qureshi T, Chaus F, Fogg L, Dasgupta M, Straus D, Byrne RW. Learning curve for the transsphenoidal endoscopic endonasal approach to pituitary tumors. Br J Neurosurg 2016;30(06):637–642
74 Thawani JP, Ramayya AG, Pisapia JM, Abdullah KG, Lee JY-K, Grady MS. Operative Strategies to Minimize Complications Following Resection of Pituitary Macroadenomas. J Neurol Surg B Skull Base 2017;78(02):184–190https://pubmed.ncbi.nlm.nih.gov/28321384
75 Lobatto DJ, de Vries F, Zamanipoor Najafabadi AH, et al. Preoperative risk factors for postoperative complications in endoscopic pituitary surgery: a systematic review. Pituitary 2018;21(01):84–97
76 Boling CC, Karnezis TT, Baker AB, et al. Multi-institutional study of risk factors for perioperative morbidity following transnasal endoscopic pituitary adenoma surgery. Int Forum Allergy Rhinol 2016;6(01):101–107
77 Zhang L, Chen M. Analysis of factors causing intracranial infection after endoscopic resection of pituitary tumors by transnasal-sphenoidal approach. Biomed Res 2014;25(04):437–440
78 Komotar RJ, Starke RM, Raper DMS, Anand VK, Schwartz TH. Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of giant pituitary adenomas. Pituitary 2012;15(02):150–159
79 de Paiva Neto MA, Vandergrift A, Fatemi N, et al. Endonasal transsphenoidal surgery and multimodality treatment for giant pituitary adenomas. Clin Endocrinol (Oxf) 2010;72(04):512–519
80 Yano S, Hide T, Shinojima N. Efficacy and Complications of Endoscopic Skull Base Surgery for Giant Pituitary Adenomas. World Neurosurg 2017;99:533–542
81 Chowdhury T, Prabhakar H, Bithal PK, Schaller B, Dash HH. Immediate postoperative complications in transsphenoidal pituitary surgery: A prospective study. Saudi J Anaesth 2014;8(03):335–341https://pubmed.ncbi.nlm.nih.gov/25191182
82 Olson DR, Guiot G, Derome P. The symptomatic empty sella. Prevention and correction via the transsphenoidal approach. J Neurosurg 1972;37(05):533–537
83 Thomé C, Zevgaridis D. Delayed visual deterioration after pituitary surgery–a review introducing the concept of vascular compression of the optic pathways. Acta Neurochir (Wien) 2004;146(10):1131–1135, discussion 1135–1136
84 Barzaghi LR, Donofrio CA, Panni P, Losa M, Mortini P. Treatment of empty sella associated with visual impairment: a systematic review of chiasmapexy techniques. Pituitary 2018;21(01):98–106
85 Chen X, Huang W, Li H, et al. Comparison of outcomes between endoscopic and microscopic transsphenoidal surgery for the treatment of pituitary adenoma: a meta-analysis. Gland Surg 2020;9(06):2162–2174https://pubmed.ncbi.nlm.nih.gov/33447567

Circumbilical Access for Ventriculoperitoneal Bypass Insertion in Adults

Acesso Circumbilical para Inserção de Derivação Ventriculoperitoneal em Adultos

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Abstract

Introduction The use of a minilaparotomy for catheter implantation can bring important complications such as adhesions, intestinal lesions, incisional hernias and postoperative pain. In neurosurgery, the umbilical access, currently widely used by surgeons of different specialties mainly for its aesthetic results, is still restricted by the unfamiliarity of the access.

Material and Method During the period between 2019 and 2020, a total of 12 patients who required ventricular bypass were selected, using circumbilical access for insertion of the peritoneal catheter and followed up for 12 months to analyze possible complications.

Description of the Technique The surgeon responsible for the abdomen performs an umbilical incision bordering the upper edge of the upper ring, avoiding the mamelon, quickly finding the linea alba under the umbilical plane, which after dissection allows reaching the peritoneum, without breaking the rectus muscles. The peritoneum can then be opened under visual control.

Results All patients presented resolution of hydrocephalus with good aesthetic results and without complications.

Discussion The aesthetic result of the transumbilical procedure was the stimulus for the development of the technique that proved to be easy, safe, cheap, and aesthetic. Initially, the ease of access to the peritoneal cavity is clear, in addition to avoiding manipulation of the rectus abdominis muscle, which improves postoperative pain.

Conclusion The circumbilical access for the implantation of a ventriculoperitoneal shunt is safe, effective and has a better aesthetic result for adult patients and should be part of the operative arsenal of neurosurgeons.

Keywords

- ventriculoperitoneal shunt
- hydrocephalus
- umbilicus

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Resumo

Introdução O uso de uma minilaparotomia para o implante do cateter pode trazer importantes complicações como adesões, lesões intestinais, hérnias incisionais e dor pós operatória. O acesso umbilical, atualmente muito utilizado por cirurgiões de diversas especialidades principalmente por seus resultados estéticos, na neurocirurgia ainda é restrito pela não familiaridade do acesso.

Material e Método Foram selecionados 12 pacientes, durante o período de 2019 e 2020, que necessitavam de derivação ventricular, sendo utilizada o acesso circumbilical para inserção do cateter peritoneal e acompanhada por doze meses para analise de possíveis complicações.

Descrição da Técnica O cirurgião responsável pelo abdome realiza uma incisão umbilical margeando a borda superior no rodete superior, fugindo do mamelão, encontrando rapidamente a linha alba sob o plano umbilical que após dissecção permite-se chegar ao peritônio, sem romper os músculos retos. O peritônio pode então ser aberto sob controle visual.

Resultados Todos os pacientes apresentaram resolução da hidrocefalia com bom resultado estético e sem complicações.

Discussão O resultado estético do procedimento transumbilical foi o estímulo para o desenvolvimento da técnica que se mostrou fácil, segura, barata e estética. Inicialmente é nítido a facilidade do acesso à cavidade peritoneal, além de evitar a manipulação do musculo reto abdominal, o que melhora a dor pós-operatória.

Conclusão O acesso circumbilical para a implantação de derivação ventriculoperitoneal é seguro, efetivo e possui melhor resultado estético para pacientes adultos, devendo fazer parte do arsenal operatório de neurocirurgiões.

Palavras-chave

- derivação ventriculoperitoneal
- hidrocefalia
- umbigo

Introduction

The treatment of hydrocephalus is part of a neurosurgeon's routine, and ventriculoperitoneal shunt is a popular option due to the familiarity of the procedure. This procedure is classically described with the performance of a paraumbilical incision and opening of the rectus abdominis muscle. However, the use of a minilaparotomy for catheter implantation can bring important complications such as adhesions, intestinal lesions, incisional hernias and postoperative pain[1]

With these complications in mind, the umbilical approach was initially described in 1986[1,2] and is currently widely used by surgeons from different specialties, mainly for its aesthetic results. In neurosurgery, its use is still restricted by the unfamiliarity of access.

Thus, the present article aimed to analyze the outcome of the technique of insertion of ventriculoperitoneal shunts in adults using circumbilical access.

Material and Method

Externally, the umbilicus consists of an infundibulum, being surrounded by the rodete, which is an elevated external margin. The fall of the umbilical stump leaves a scar on the underside that may be situated in or near a shallow depression in the skin, called a sulcus. The mamelus is considered to be a remnant of the solid parts of the umbilical cord, being a prominent area that contained the urachus and umbilical arteries. The normal umbilicus has a wide variety of intermediate forms, and each component mentioned may or may not be present.[3]

The navel, on its internal surface, is free, being separated by the parietal peritoneum from the abdominal cavity, having only one umbilical fascia with variable thickness. The function of this ring is to reinforce the peritoneum, its margins being formed by the union of the oblique fascia in the aponeurosis of the linea alba. Superiorly, its border is free, but inferiorly it receives the insertion of the umbilical and urachus arteries, which in the adult form the medial and median umbilical ligaments, respectively.

Twelve patients with a mean age of 54 years old who required ventricular shunt were selected, during the period between 2019 and 2020, 8 of them women, for the following causes: posterior fossa tumors, subarachnoid hemorrhage, normal pressure hydrocephalus and pseudotumor cerebri.

As an exclusion criterion for the procedure, in addition to the criteria for implantation of a ventriculoperitoneal shunt, patients with previous abdominal surgeries or with umbilical herniations were considered.

After the surgery, the patient remained hospitalized for 24 hours and during this period a cranial and abdominal computed tomography (CT) was performed to verify an adequate positioning of the two ends of the catheter. Within a period of 14 days, the removal of the cranial suture was scheduled, and outpatient follow-up remained quarterly in the first year after surgery.

After the procedure, the patients were followed-up for 12 months, being questioned about the aesthetic result and investigated for possible complications such as abdominal pain, infection, and incisional hernia.

Technique Description

Surgery performed by two neurosurgeons, one responsible for the skull and the other for the abdomen. Initially, the patients were positioned in dorsal decubitus with their head on a rotational caster contralateral to the puncture site and a pad on the ipsilateral shoulder. Afterwards, marking, shaving and asepsis are performed with degerming and alcoholic chlorhexidine according to protocols,[4] paying special attention to the umbilicus, in addition to antibiotic prophylaxis with first-generation cephalosporin.

The surgeon responsible for the abdomen performs an umbilical incision bordering the upper edge with a scalpel n15 (►**Fig. 1A**). The incision site must be in the upper ring, avoiding the mamelon, to avoid injury to the remnants of the umbilical cord or a possible Meckel diverticulum, whose prevalence in the population varies from 0.3 to 2.9%.[5] Next, the linea alba is quickly found under the umbilical plane, which, when gradually dissected with the help of Kelly forceps, allows it to reach the peritoneum directly, without breaking the lateral straight muscles. The peritoneum can then be opened under visual control.

The incision, trepanation and cranial puncture remain identical to the traditional technique as well as the tunneling and burial of the peritoneal catheter in the peritoneal cavity (►**Fig. 1B**).

Closure is performed only with a 4.0 polyglecaprone thread in an intradermal suture technique followed by a sterile gauze dressing.

Results

The aesthetic improvement of the procedure is easily visible in the postoperative period when compared with the transrectal incision technique commonly performed. The duration of the procedure and the postoperative period were not prolonged. All patients had resolution of hydrocephalus and none complained of abdominal pain after the procedure, with an infection rate remaining at zero, as well as the rate of incisional hernia. All patients evolved uneventfully during the 12-month follow-up period and confirmed that they were satisfied with the aesthetic result of the surgery. A summary of the cases with the primary pathologies can be seen in ►**Table 1**.

Discussion

For a long time, the use of the navel to access the abdomen was avoided because it was believed to be a source of infection. But the aesthetic result of the transumbilical procedure was the stimulus for the development of the technique that proved to be easy, safe, cheap and aesthetic.[1,2,6–9] Studies show its use for cholecystectomies, appendectomies and even breast implants.[7,9,10]

Several other advantages were observed with this surgical technique, initially the ease of access to the peritoneal cavity is clear, in addition to avoiding manipulation of the rectus abdominis muscle, which improves postoperative pain. The passage of the catheter and its introduction did not present difficulties and, in addition, its passage through the midline avoided the breast tissue, an important factor for females. Closure is also simpler, as only one layer of skin needs to be sutured, without the need to suture fascia and subcutaneous tissue.

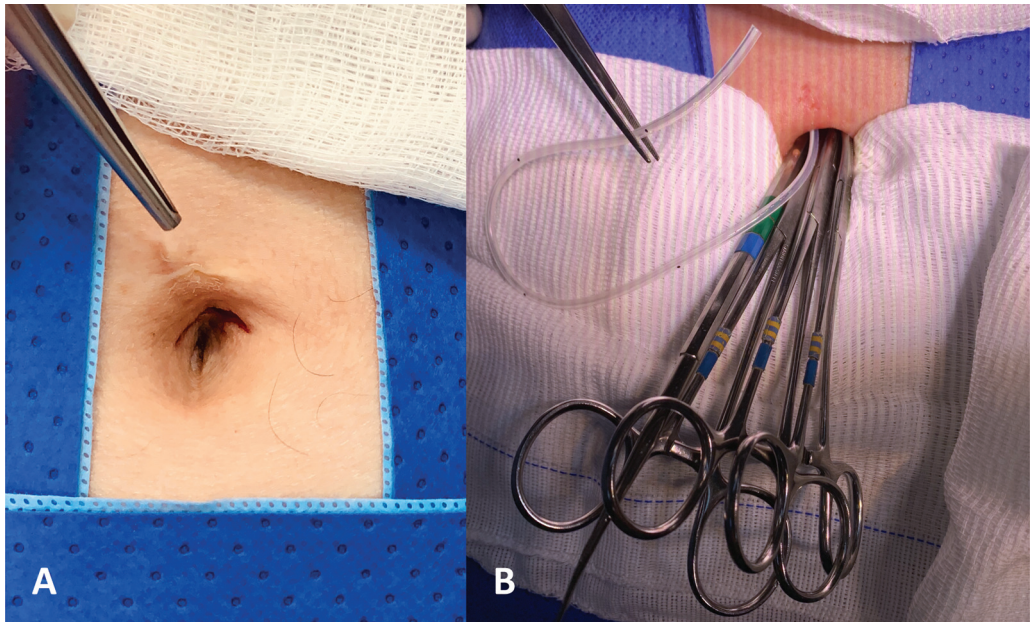

Fig. 1 (**A**) The circumbilical incision with a scalpel blade is observed; (**B**) Intraoperative appearance after tunneling the shunt catheter.

Table 1 Summary of operated cases

Patients	Gender	Age (years old)	Pathology	Postoperative infection	Incisional hernia	Aesthetic outcome
1	F	26	Posterior fossa tumor	–	–	+
2	F	67	Neurocysticercosis	–	–	+
3	F	75	Posterior fossa tumor	–	–	+
4	F	62	Subarachnoid hemorrhage	–	–	+
5	M	64	Posterior fossa tumor	–	–	+
6	F	70	Normal pressure hydrocephalus	–	–	+
7	F	48	Meningitis	–	–	+
8	M	49	Pituitary macroadenoma	–	–	+
9	F	43	Lumbar schwannoma	–	–	+
10	M	37	Pseudotumor cerebri	–	–	+
11	F	58	Posterior fossa tumor	–	–	+
12	M	59	Normal pressure hydrocephalus	–	–	+

This technique should initially be compared to the minimally invasive technique of percutaneous introduction of a Portnoy trocar. However, the circumbilical approach allows an opening of the peritoneal cavity under direct visualization, unlike the trocar that perforates the peritoneum blindly, with the risk of intestinal injury.[7]

Studies show that the risk of infection and wound dehiscence were not higher when performing an umbilical incision.[2,6–9] The risk of umbilical and incisional hernia was not reported in our series or in the literature.[6–9]

Conclusion

The circumbilical access for the implantation of a ventriculoperitoneal shunt is safe, effective, and has a better aesthetic result for adult patients, and should be part of the operative arsenal of neurosurgeons. In this series of cases presented, there were no complications reported such as infections and incisional herniations, proving to be a feasible technique for neurosurgical routine.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Recinos PF, Pindrik JA, Bedri MI, Ahn ES, Jallo GI, Recinos VR. The periumbilical approach in ventriculoperitoneal shunt placement: technique and long-term results. J Neurosurg Pediatr 2013;11 (05):558–563
2 Scavarda D, Breaud J, Khalil M, et al. Transumbilical approach for shunt insertion in the pediatric population: an improvement in cosmetic results. Childs Nerv Syst 2005;21(01):39–43
3 Fahmy M. Umbilicus and Umbilical Cord [Internet]. Cham: Springer International Publishing; 2018. Available from: http://link.springer.com/10.1007/978-3-319-62383-2
4 Villalonga JF, Giovannini S, Caffaratti G, Lorefice E, Centeno TR, Del Pont FM. Implante de shunt ventrículo peritoneal en el paciente adulto. Un nuevo protocol. Surg Neurol Int 2019;10(174, Suppl 1) S26–S36
5 Lindeman RJ, Søreide K. The Many Faces of Meckel's Diverticulum: Update on Management in Incidental and Symptomatic Patients. Curr Gastroenterol Rep 2020;22(01):3
6 Tubbs RS, Azih LC, Mortazavi MM, et al. Transumbilical approach for ventriculoperitoneal shunt placement in infants and small children: a 6-year experience. Childs Nerv Syst 2012;28(02): 217–219
7 Litré CF, Noudel R, Scavarda D, et al. [Trans-umbilical access and ventriculoperitoneal shunt in adults: preliminary results]. Neurochirurgie 2007;53(04):307–311
8 Lee JS, Hong TH, Kim JG. A comparison of the periumbilical incision and the intraumbilical incision in laparoscopic appendectomy. J Korean Surg Soc 2012;83(06):360–366
9 Suri M, Langer JC. A comparison of circumumbilical and transverse abdominal incisions for neonatal abdominal surgery. J Pediatr Surg 2011;46(06):1076–1080. Doi: 10.1016/j.jpedsurg.2011.03.032
10 Blanco FC, Kane TD. Single-port laparoscopic surgery in children: concept and controversies of the new technique. Minim Invasive Surg 2012;2012:232347

Pituitary Hormonal Disturbances in Aneurysmal Subarachnoid Hemorrhage

Distúrbios hormonais pituitários na hemorragia subaracnóidea aneurismática

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Abstract

Objective The objective of the present study was to assess the hormonal alterations that occurred in patients with subarachnoid hemorrhage.

Methods This is a case series with 21 patients diagnosed with subarachnoid hemorrhage of aneurysmal etiology up to 30 days after the ictus. The following hormonal measurements were performed in these patients: cortisol, GH, testosterone, prolactin, estradiol, FSH, LH, FSH, T3, T4 and free T4. The hormonal results of the cases were compared with the results of twelve volunteers from the control group and correlated with findings in brain tomography, cerebral angiography, Hunt-Hess scale, and vasospasm.

Results The main altered hormones were cortisol (52.6%), GH (42.9%) and TSH (28.6%). There was a trend towards more severe cases in the following groups of patients: Hunt-Hess scale > 2, Fisher scale > 1, aneurysmal topography in the anterior communicating artery and those who had vasospasm.

Conclusion The present study observed the tendency of pituitary hormonal changes in patients with subarachnoid hemorrhage of aneurysmal etiology, corroborating the need for dosage of hormones from the hypothalamic-pituitary axis in the management of these cases.

Keywords
- pituitary gland
- pan-hypopituitarism
- subarachnoid hemorrhage
- hormone abnormalities
- intracranial aneurysm

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Resumo

Objetivo O objetivo do presente estudo foi avaliar as alterações hormonais em pacientes com hemorragia subaracnóidea e correlacionar tais alterações com a gravidade da hemorragia.

Métodos Trata-se de uma série de casos com 21 pacientes com diagnóstico de hemorragia subaracnóidea de etiologia aneurismática até 30 dias do ictus. Foram realizadas as seguintes dosagens hormonais nesses pacientes: cortisol, GH, testosterona, prolactina, estradiol, FSH, LH, FSH, T3, T4 e T4 livre. Os resultados hormonais dos casos foram comparados com os resultados de 12 voluntários do grupo controle e correlacionados com achados em tomografia de crânio, estudo angiográfico cerebral, escala de Hunt-Hess e vasoespasmo.

Resultados Os principais hormônios alterados foram o cortisol (52,6%), GH (42,9%) e o TSH (28,6%). Houve uma tendência de casos mais graves nos seguintes grupos de pacientes: escala de Hunt-Hess > 2, escala de Fisher > 1, topografia aneurismática na artéria comunicante anterior e aqueles que cursaram com o vasoespasmo.

Conclusão O presente estudo observou a tendência de alterações hormonais hipofisárias em pacientes com hemorragia subaracnóidea de etiologia aneurismática, corroborando a necessidade de dosagem dos hormônios do eixo hipotálamo-hipofisário no manejo desses casos.

Palavras-chave

- hipófise
- pan-hipopituitarismo
- hemorragia subaracnóidea
- anormalidades hormonais
- aneurisma intracraniano

Introduction

Hormonal changes associated with hypothalamic-pituitary dysfunction may occur during subarachnoid hemorrhage or as a result of mass effect on the hypothalamus-pituitary exerted by cerebral aneurysms.[1,2]

The first description of pituitary dysfunction associated with the presence of an intracranial aneurysm was reported in 1887 by Bramwell.[3] This author reported the case of a man with 31 years and a history of cognitive disorder, habit, decreased vision, decreased head and pubic hair, testicular atrophy, and gynecomastia. At the time of autopsy, an aneurysm of the internal carotid artery was diagnosed, related to the sella turcica and its content, that is, the pituitary gland.[3]

Horn brook and Marks, in 1961, studied three women with hypopituitarism associated with intracranial aneurysm, and raised the hypothesis that pituitary dysfunction is a consequence of the interference of the aneurysm with the blood supply of the hypothalamic nuclei.[4] All the patients improved with hormone replacement.

We stress that even though historical records suggest a possible hormonal dysfunction with the presence of intracranial aneurysms, there are few studies evaluating pituitary function after aneurysmal subarachnoid hemorrhage (SAH).

The present study aimed to assess possible hormonal changes in patients who suffered intracranial aneurysm rupture.

Methods

We conducted a prospective study involving 21 patients diagnosed with SAH by rupturing an intracranial aneurysm in the Hospital da Restauração, Recife, state of Pernambuco, Brazil. One hundred and thirty-five blood collections were made, and in 5 patients, the blood samples were made in the pre- and postoperative periods, totaling 1,350 hormonal dosages.

The inclusion criterion was based on the choice of patients with SAH due to a rupture of a cerebral aneurysm that occurred in a period not exceeding 30 days, made by clinical history, brain computed tomography (CT) and cerebral digital angiography. The present study did not include subjects with known endocrine diseases, such as diabetes mellitus.

In all patients, the insulin tolerance test was performed to stimulate GH and cortisol production. The test was protocol with the injection of 0.1 IU/kg insulin (simple), intravenously just after the first blood baseline sample, followed up with a serial collection of samples after 30, 60, 90, and 120 minutes. Before the test, patients remained fasting for 10 hours.

All patients underwent brain CT and cerebral angiography by femoral catheterization.

The values were compared with the reference values and revalidated for conducting the tests on 12 healthy volunteers, 6 men and 6 women, who were known as the control group.

Patients were classified according to the Fisher scale, and after being clinically examined, they were also classified according to the graduation of Hunt & Hess.

In all patients, cerebral tomography was performed to exclude other complications. A digital cerebral angiography confirmed the presence and location of aneurysms.

In five patients, the collection was made pre-and postoperatively, which has given us an opinion on the influence of surgical management in these patients.

For the present work, a design type series of cases was performed. The research was approved by the Ethics Committee of Universidade Federal de Pernambuco (Protocol 227/2002-CEP/CCS) and by the Ethics Committee of the

Hospital da Restauração of Recife. All patients or family are aware of the rules of the research and signed the written informed consent.

The average age of the patients was 48 years old with a median of 50 years old. We used the technique of mathematical logic to extend the model of the network of causes, multivariate analysis, associated with the separation of groups into subgroups or stratum, stratification was observed and the relationship between the dependent variables (hormonal changes) and the independent variables (location of aneurysms, the Hunt & Hess classification, classification of Fisher and the presence of symptomatic cerebral vasospasm).

Statistical Analysis

We applied the statistical test of Kolmogorov-Smirnov to determine the type of distribution of variables to be studied and found that they had non normal distribution. In view of this, we used the nonparametric Mann-Whitney or Kruskal-Wallis tests. In the analysis of categorical variables, we used the Fisher exact test as an alternative to the X2 test (chi-squared), characterizing the level of significance as $< 5\%$ ($p < 0.05$).

Results

The hormone concentrations found in patients with subarachnoid hemorrhage in a period of 30 days after the rupture of aneurysms are shown in ►**Table 1** and ►**Table 2**.

The hormone concentrations found in each of the 21 patients were compared with the normal reference hormonal assay values reported by the laboratory and the values found in the control group (►**Table 3**).

We found abnormalities in most of the hormones studied compared with the reference values of the hormonal assay tests and observed in the control group, with the exception of estradiol, in which no change was observed in any of our patients.

The hormone cortisol is the most changed, and this happened in 52.4% of patients, followed by 42.9% in GH, 28.6% in TSH, 23.8% in T3, 9.5% in prolactin, 9.5% in free T4 and LH, and 4.8% in FSH and T4.

The serum concentration of testosterone was measured in 4 male subjects, and in 3 (75%) it was below normal levels.

It was found that TSH (►**Figure 1**) and GH (►**Figure 2**) showed statistically significant changes ($p < 0.05$). The other hormones, T3, T4, free T4, prolactin, and cortisol, had no statistical differences compared with reference values. The concentration of LH was not significantly affected ($p = 0.114$).

Most of the hormones studied showed changes in deficit, except for patients 5 and 8, in whom the concentrations of basal cortisol and PRL (Prolactin) increased. The importance of ITT (insuline tolarence test) is well-reflected in the changes observed in GH and cortisol, which revealed normal basal concentrations, but inadequate responses to stimulation (patients #3, 4, 5, 6, 11, 12, 13, 14, 15, 16, 18, 19, and 20).

Of the patients studied, the Hunt & Hess classification was 2 (52.4%), 1 (23.8%), 3 (14.3%), and 4 (9.5%). The severity of the subarachnoid hemorrhage was classified in our study according to the scale established by Fisher in 1980 on the CT findings. Three patients were classified with grade 1 (14.3%), 9 patients with grade 2 (42.9%), 6 patients with grade 3 (28.6%), and 3 patients with grade 4 (14.3%).

Aneurysms located in the posterior communicating artery were observed in 8 individuals, equivalent to 42.8% of the sample. The other locations were the middle cerebral artery ($n = 5$; 24.0%), the anterior communicating artery ($n = 5$; 24.0%) and the pericallosal, the basilar, and the posterior inferior cerebellar arteries, with a patient for each of the arteries.

Six out of 21 (28.6%) patients had a history of symptomatic cerebral vasospasm, characterized by somnolence and new motor deficit. Despite the clinical picture of symptomatic vasospasm, all patients progressed to stability and the surgery was uneventful.

Regarding the severity of symptoms of patients with subarachnoid hemorrhage by rupture of cerebral aneurysm, according to the Hunt & Hess scale, hormonal disorder was observed in patients with the more severe clinical picture, Hunt & Hess ≥ 3 with the free T4 ($p = 0.043$). There were also trend changes in T3, TSH, and GH ($p = 0.1$). Sixteen patients presented a Hunt & Hess classification of < 3, and 9 showed hormonal changes corresponding to 56.3% of the sample.

In the Hunt & Hess classification ≥ 3, all 5 patients showed hormonal changes, that is, 100% (patients #5, 6, 8, 13, and 20). According to the Fisher CT classification of subarachnoid hemorrhage used in the present study, we observed significantly higher hormonal disorder in patients with more severe classification in the scale, that is, Fisher 3 and 4, especially for T3 and GH hormones ($p < 0.05$).

Regarding the location of the aneurysm after SAH and the hormonal changes, there was no statistical difference concerning its position, with a slightly greater number of altered hormones in patients with aneurysms located in the anterior communicating artery.

Correlating the hormonal changes due to the subarachnoid hemorrhage of aneurysms located in the polygon of Willis and aneurysms in other locations, the differences were not significant ($p > 0.05$; Fisher exact test). Hormonal changes in the secretion of GH were observed in patients with cerebral vasospasm ($p = 0.041$; Fisher exact test).

From a total of 6 patients with symptomatic vasospasm, 5 (83.3%) showed hormonal changes. The patients with symptomatic vasospasm were numbers 4, 5, 11, 13, 15, and 20. Out of 15 patients who had no vasospasm, 5 showed hormonal changes, representing 33.33% of the cases.

Stratify the patients who presented clinical data compatible with the classification of Hunt & Hess ≥ 3, with patients classified as Fisher ≥ 2, and had cerebral vasospasm; we observed the patient numbers 5, 11, 13, and 20. Of these, three patients (numbers 11, 13 and 20) had an aneurysm of the anterior communicating artery, and there was a higher percentage of hormonal changes in these patients. We

Table 1 Individual data of 21 patients with SAH related to age, genus, and score of the classification of Hunt & Hess, score of the classification of subarachnoid hemorrhage on CT cerebral Fisher and basal concentrations of the following hormones: TSH, T3, T4, FT4, LH, FSH, TESTOSTERONE, ESTRADIOL, PROLACTIN, GH and CORTISOL

Case	Age (years old)/ Sex	Hunt-Hess	Fisher	Angiography	Vasoespasm	TSH (uIU/ml)	T3 (ng/dL)	T4 (ng/dl)	FT4 (ng/dl)	LH (IU/mL)	FSH (IU/mL)	TES (ng/dl)	E2 (pg/mL)	PRL (ng/mL)	GH (ng/ml)	Cortisol (mcg/dL)
1	50/W	II	II	R PComm	No	0.30	80.00	6.40	0.81	24.20	83.10	–	<20.00	6.80	0.12	1.30
2	39/W	II	II	R PICA	No	0.97	86.50	7.10	1.00	6.50	3.60	–	42.30	12.70	0.35	7.70
3	37/M	II	III	ACom	No	0.10	80.80	9.30	1.40	1.50	5.90	53.90	–	3.30	0.16	3.90
4	50/W	II	III	L MCA + L PComm + R PComm	Yes	0.73	46.30	9.70	1.10	15.00	47.80	–	<20.00	15.50	0.31	1.70
5	55/W	IV	III	L MCA	Yes	0.20	48.30	9.80	0.95	21.00	50.60	–	<20.00	51.90	0.91	90.50
6	74/W	III	II	Top of basilar	No	0.63	58.50	6.70	0.68	23.90	65.70	–	31.90	17.00	0.46	25.60
7	58/M	I	II	L Pericalosal	No	0.51	83.50	8.10	1.20	3.10	40.80	–	<20.00	12.70	0.23	11.70
8	40/W	I	III	R MCA	No	0.70	99.60	9.70	1.30	4.20	1.40	113.00	–	78.90	0.41	57.30
9	41/W	I	III	R MCA	No	0.68	77.00	6.10	1.00	1.40	1.20	–	129.00	18.30	0.29	1.70
10	50/M	II	IV	R MCA	No	0.31	84.9	6.90	1.00	3.50	7.20	–	31.90	10.50	0.49	16.50
11	73/M	III	III	ACom	Yes	0.52	100.00	7.40	1.00	3.70	4.40	228.00	–	10.20	1.30	33.90
12	16/M	I	I	R PComm	No	1.27	71.20	6.10	1.10	0.90	1.60	<50.00	–	8.50	1.40	32.50
13	63/W	IV	IV	ACom	Yes	0.21	<40.00	1.20	0.26	0.60	30.90	–	<20.00	9.50	0.54	28.70
14	50/W	II	II	R MCA	No	0.57	92.20	11.00	1.00	7.70	16.90	–	61.60	9.70	1.00	16.10
15	58/W	II	IV	L PComm	Yes	2.45	98.00	7.30	1.30	17.60	65.60	–	<20.00	14.60	0.62	14.60
16	44/W	I	I	R PComm + OA	No	0.47	80.00	4.90	0.93	2.20	2.40	–	45.00	7.00	0.64	1.40
17	46/W	II	II	R PComm	No	0.12	70.00	6.30	0.87	3.90	9.30	–	<20.00	17.80	0.46	5.30
18	30/W	II	II	ACom	No	0.88	76.60	8.20	1.10	0.20	0.20	–	35.10	12.00	1.70	28.70
19	52/W	II	II	R PComm	No	0.82	<40.00	8.60	1.20	47.70	43.90	–	33.70	2.10	0.19	2.00
20	44/W	III	I	ACom	Yes	1.23	97.00	9.50	1.00	2.50	23.80	–	51.30	12.10	0.04	9.80
21	43/W	II	II	L PComm	No	2.20	93.90	6.90	1.20	2.30	9.70	–	88.4	3.10	0.15	16.40

Abbreviations: ACom, anterior communicating artery; CT, computed tomography; E2, estradiol; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; L, left; LH, luteinizing hormone; M, man; MCA, middle cerebral artery; OA, ophthalmic artery; PComm, posterior communicating artery; PICA, posterior inferior cerebellar artery; PRL, prolactin; R, right; SAH, subarachnoid hemorrhage; T3, triiodothyronine; T4, thyroxine; TES, testosterone; TSH, thyroid stimulating hormone; W, woman.

Table 2 Individual values of hormonal concentrations of prolactin, growth hormone, and cortisol, detected in 21 individuals after the insulin tolerance test, and blood collections were taken at 30, 60, 90, and 120 minutes

	Prolactin (ng/mL)				Growth hormone (ng/ml)				Cortisol (mcg/dL)			
Case	30 minutes	60 minutes	90 minutes	120 minutes	30 minutes	60 minutes	90 minutes	120 minutes	30 minutes	60 minutes	90 minutes	120 minutes
1	9.20	13.20	8.80	8.70	0.16	0.71	3.80	4.10	8.10	4.00	1.40	1.50
2	10.40	9.20	9.80	7.40	3.00	1.70	1.00	1.00	15.90	13.80	13.20	11.00
3	2.60	5.50	6.80	6.80	0.14	0.15	0.30	0.18	3.10	3.20	2.70	2.70
4	13.30	12.90	12.40	14.60	0.30	0.19	0.42	0.45	1.30	1.40	1.50	1.30
5	53.90	53.80	51.80	49.70	0.96	1.00	0.82	0.63	96.40	93.70	89.70	40.80
6	10.00	9.90	6.90	4.30	0.64	0.39	0.47	0.56	26.90	25.90	32.10	34.50
7	11.10	9.10	7.80	12.80	13.10	3.10	0.84	0.45	11.80	17.40	18.70	17.60
8	75.50	74.60	76.70	78.80	6.40	3.64	2.80	1.73	53.40	54.70	60.00	33.70
9	11.10	19.70	18.40	17.50	6.60	3.10	0.42	0.24	2.40	9.70	6.50	1.70
10	10.30	11.90	12.90	12.60	7.15	6.55	4.52	0.42	16.00	19.10	28.90	22.40
11	10.30	20.20	21.40	20.30	9.40	8.50	5.40	3.50	29.50	31.30	35.10	27.30
12	6.90	8.60	10.30	9.60	5.40	2.90	3.90	4.10	16.50	19.40	21.40	12.50
13	5.90	3.30	3.60	3.60	0.72	0.72	0.71	0.62	23.80	25.60	32.90	29.30
14	8.80	16.70	16.80	16.40	3.00	6.70	6.00	6.00	13.00	7.80	8.10	6.30
15	11.20	17.30	38.10	29.10	1.20	1.00	1.80	1.10	16.90	15.40	11.80	15.70
16	9.20	9.40	11.40	10.70	0.53	2.60	5.20	3.60	1.70	1.00	2.20	1.30
17	20.30	17.00	16.00	15.00	5.48	3.90	3.60	3.39	12.10	10.30	9.10	8.70
18	9.00	17.30	5.40	10.30	1.20	1.44	1.60	1.31	33.60	39.70	35.40	33.50
19	5.90	2.10	4.70	4.40	0.23	1.00	0.53	0.50	37.40	34.80	29.30	24.20
20	12.10	13.10	17.40	14.20	0.08	0.80	1.40	0.41	8.10	9.20	8.40	7.60
21	2.20	2.10	1.90	1.50	0.39	10.5	6.50	2.90	10.10	15.00	21.20	17.50

Table 3 Results of tests performed on 12 healthy volunteers

Case	Age (yearsold)/ Sex	T3 (ng/dL)	T4 (ng/dL)	TSH (uIU/ml)	FT4 (ng/dl)	FSH (IU/mL)	LH (IU/mL)	PRL (ng/mL)	E2 (pg/mL)	TES (ng/dl)	GH (ng/ml)	CORTISOL (mcg/dL)
1	53/W	112.00	8.90	2.35	1.00	6.80	2.40	13.00	134.00	–	2.20	17.50
2	55/W	68.90	5.90	1.00	1.10	99.60	23.10	13.30	44.50	–	2.20	9.80
3	51/W	85.80	6.50	1.55	1.20	56.50	24.60	5.40	51.50	–	1.00	5.80
4	45/W	75.40	6.00	0.60	1.00	33.60	13.40	3.60	45.20	–	0.19	11.60
5	50/W	66.30	8.60	0.92	1.00	141.00	55.50	9.70	47.80	–	0.17	2.70
6	36/W	88.10	8.20	01.05	1.20	5.70	8.10	7.70	301	–	0.08	15.90
7	48/M	91.90	4.90	1.16	1.20	2.90	1.10	3.40	–	511.00	0.05	8.10
8	68/M	107.00	9.70	0.64	1.10	7.00	4.70	2.20	–	572.00	0.75	13.00
9	52/M	93.50	6.60	01.09	1.00	1.20	0.50	8.70	–	320.00	0.06	8.80
10	47/M	62.50	8.50	0.90	1.30	1.30	2.10	8.10	–	608.00	0.05	11.60
11	63/M	70.20	7.40	0.82	1.40	8.70	2.00	17.00	–	677.00	0.05	10.50
12	45/M	83.90	5.80	02.05	1.10	5.50	1.90	6.10	–	677.00	0.05	10.50

Abbreviations: E2, estradiol; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; L, left; LH, luteinizing hormone; M, man; PRL, prolactin; R, right; T3, triiodothyronine; T4, thyroxine; TES, testosterone; TSH, thyroid stimulating hormone; W, woman.

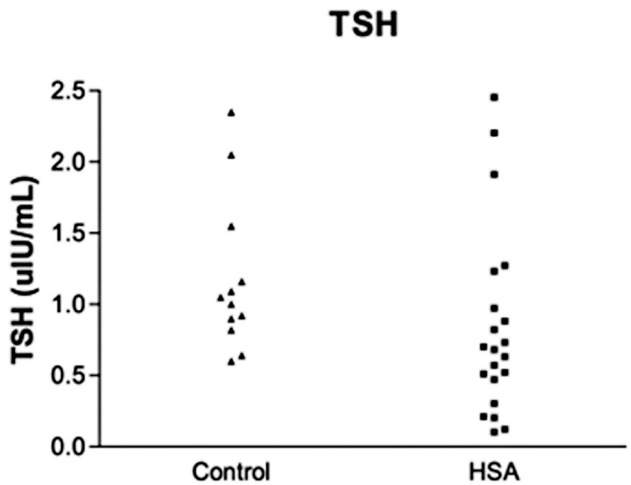

Fig. 1 Comparison between the control group and patients with SAH in the basal dosage of serum TSH ($p = 0.033$).

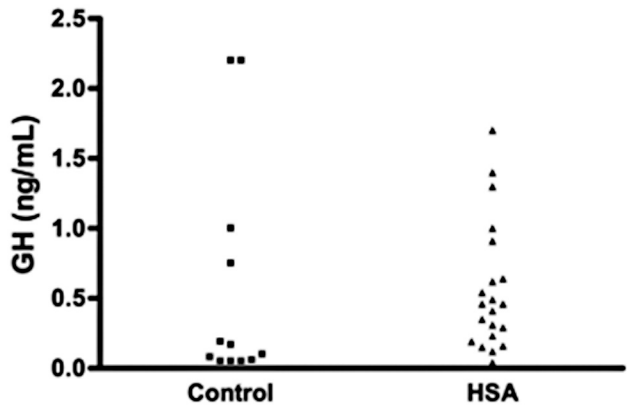

Fig. 2 Comparison between the control group (healthy) and patients with SAH regarding GH ($p = 0.001$).

analyzed the postoperative hormonal dosages in five patients, and normalization occurred in most hormones.

Discussion

Six (29%) of our 21 patients developed cerebral vasospasm with clinical significance of the transient worsening level of consciousness and motor deficit persisting until hospital discharge. These patients had a greater tendency for hormonal changes, and perhaps more significant damage to the hypothalamus-pituitary occurred, consequent to ischemia and increased intracranial pressure.[5]

Our study found 52.4% of patients with changes in cortisol; the majority observed only after the test stimulation of insulin, when there was the expected increase in subsequent doses of 7µg/dl. A subarachnoid hemorrhage by rupture of cerebral aneurysm is the cause of psychological stress, as well as the stress or pain due to increased intracranial pressure.[6] In situations of stress, it is well known that secret the hormone stimulating hypothalamus of corticotropin, which stimulates the pituitary to produce ACTH and the adrenal cortex to stimulate the production of cortisol.[7] With

this condition, it was to be expected that, in this case, find a greater number of patients with increased cortisol. Likely lock in hypothalamus-pituitary axis is involved in our results, as well as specific lesions of the nucleus arched (arcuate) in the tuberal region of the hypothalamus may be involved.[4] Edwards et al.[8] found in their six patients with head trauma, lack of cortisol response to stimulation with the ITT (insuline tolarence test) (0.01 IU / kg), TRH (Thyrotropin-releasing hormone) (200µg) and GnRH (Gonadotropin-releasing hormone) (100µg). Concluded that possible mechanisms are involved, such as direct injury of the hypothalamus by blood in the subarachnoid space, injury to the hypothalamic-pituitary stem the increase in intracranial pressure and decreased cerebral perfusion pressure, or consequent to cerebral vasospasm.[9]

Crompton,[10] in anatomical studies of autopsies of patients with rupture of cerebral aneurysm, observed hypothalamic lesions in 61% of the brains studied. In 2 patients, numbers 5 and 8, we found increased cortisol and prolactin, which is considered a normal response to situations of stress. The prolactin was increased by 9.52% of our patients. It is known that prolactin increases rapidly in situations of stress (2 to 3 times the baseline) and that in 24 hours it returns to normal, as demonstrated in the work of Noel et al.[11] The persistence of hyperprolactinemia may be due to lack of inhibition by damage to the hypothalamus, as demonstrated by Verbalis et al.[12] The other hormonal changes in this study were deficiency in gonadotrophin, thyrotropin, GH and cortisol, data that were also found by other authors.[8,12–15]

The hypothalamic-pituitary-adrenal function, after subarachnoid hemorrhage by rupture of aneurysm, has been evaluated by the diurnal variation of the concentration level of plasma cortisol.[16] The value of plasma cortisol is considered normal when the difference between the highest and lowest dosage from the morning to the afternoon is > 6.4 µg/100ml.[17,18] An abnormal diurnal variation would be a hypothalamic injury, but Jenkins et al.[13] studied 18 patients with SAH by rupture of anterior communicating artery aneurysm with metyrapone test, pyrogen test, and test of suppression with dexamethasone, observing abnormal changes in the diurnal cortisol concentration, control of overhead power and reaction to stress. These authors found normal reaction to stress with the pyrogen test and abnormal response to metyrapone (circadian rhythm). Similar response was found by Krieger[20] using the ITT. They concluded that different sites in the hypothalamus are responsible for the increase in the cortisol response to stress, the circadian rhythm, and the control of feedback. These findings explain the variations in hormonal changes when the subarachnoid hemorrhage affects the hypothalamus. The exact location of these areas has not been determined in humans.[19]

In our study, we found hormonal changes with a predominance of the deficient hormones studied, which is in agreement with other studies.[10,20] Gonadotroph hormones are usually reduced in stressful situations, likely by a hypothalamic effect.[21] Several mechanisms may be involved: the use of illicit drugs, dopamine, glucocorticoids, and opioids may also result in lower levels of gonadotroph hormones (LH, FSH, and thus testosterone, progesterone, and estrogen).[22]

In our study, we found 75% of men with low testosterone. We found no changes in estradiol. A decrease of LH was found in 9.5% of patients and a decrease of 4.6% of FSH were observed in this series. These findings disagree with the literature that indicates a percentage of 67.5% of changes.[15] Despite these studies having emphasized the hormonal changes found in patients with rupture of cerebral aneurysm caused by subarachnoid hemorrhage, Osterman[23] evaluated the hormonal function of 50 patients with SAH and cerebral aneurysm in one, due to arteriovenous malformation and occipital pattern found normal circadian cortisol in 47 patients. The function and levels of gonadotropin were normal in all patients. These patients were examined 105 days after subarachnoid hemorrhage.

The findings of Osterman[23] disagree with the literature review by Fernández-Real et al.[15] These authors investigated the pituitary dysfunction caused by aneurysm of the carotid artery, as follows: pituitary gonadal dysfunction in 67.5% of cases, pituitary-adrenal in 48.6%, and pituitary-thyroid in 40.5% of cases.

Analyzing the results of our study, patients who presented with greater clinical severity (Hunt & Hess ≥ 3) showed a greater number of hormonal changes; however, statistically, only free T4 was significantly different ($p = 0.0476$) when compared with the group of Hunt & Hess 1 and 2. As for CT findings, according to Fisher's classification, major hormonal changes were observed in patients with Fisher CT classified as 3 and 4, and the hormone GH was statistically significant ($p = 0.0004$), as well as T3 ($p = 0.0062$). We also observed a greater tendency for hormonal changes in patients with aneurysms located in the anterior communicating artery, and those who had cerebral vasospasm, and in the latter, GH was statistically significant ($p = 0.0464$).

After stress, the GH tends to increase the metabolism by releasing of peptides (somatomedina)[24] In our study, we found 42.8% of patients with decreased GH response to stimulation with insulin. Some authors suggest that the decrease in the production of GH, which also occurs in severe head injuries, is caused by direct damage to the hypothalamus or by vascular spasms.[11,18,25] Colon et al.[25] showed the importance of GH on cognitive function in adults, showing the great importance of the preservation of these hormones at all ages.

Stress reduces the level of TSH and increases the level of cortisol.[26] Mangieri et al.[27] examined the hormonal changes of 38 patients with SAH caused by rupture of cerebral aneurysms within the first 24 hours after SAH, and observed an increase in cortisol in all patients, increased prolactin in 14.2% of patients, normal levels of FSH and LH and increased levels of TSH in 14.2% of patients, concluding that the hormonal abnormalities observed in measurements may be due to the stress caused by intracranial bleeding.

The decrease in the level of TSH in a patient under stress is due to the production of interleukin I and somatostatin,

as well as the result of increased cortisol.[28] Peters et al.[29] demonstrated that in peripheral tissues, there is metabolism of T4 to T3 by the type 1 deiodinase enzyme, which is blocked by cortisol under stress. Gupta et al.[30] reported that central hypothyroidism is characterized by low thyroid hormone with good response to stimulation of TSH to TRH, which reflects lack of stimulation of the hypothalamus.

We found in our study a decrease of 28.57% of patients for TSH, 23.80% for T3, T4 to 9.52% and 4.76% for free T4. Patients number 1, 10, and 17 showed decreased TSH and normal levels of T3, T4 and free T4, which is consistent with reaction to stress. Patients number 5 and 13 showed low levels of TSH, T3, T4 and free T4. We don't found justification for such an occurrence. Although these findings are true from the perspective of percentage, one should be careful with their interpretation, since hormonal changes are not statistically significant, with a confidence interval (CI) of 95% ($p < 0.05$) in TSH hormones, testosterone, and GH.

Other factors of importance related to our research are the recent published work showing the great relationship between quality of life, with improvement of cognitive functions (affection, mood, memory, etc.) and treatment of specific hormonal deficiency, avoiding in some cases, the frequent downtime and dementia in patients with deficiency of this hormone.[31,32]

Disorders of sodium balance after SAH are common electrolyte disturbances. Hyponatremia can affect up to 55% of patients with SAH and tends to be more frequent than hypernatremia.[33,34] Hypernatremia occurs in 20% of patients with SAH.[33] Both sodium disorders are associated with worse neurological outcomes, especially hypernatremia.[35–39] Furthermore, a recent cohort study showed that greater variability of sodium concentration is also associated with poor neurological outcome.[40] However, sodium disorders are apparently not associated with an increased risk of vasospasm after SAH.[39]

The present research report provides the risk factors for the development of hormonal changes in patients with SAH due to rupture of a cerebral aneurysm;

a) The higher the ranking by the clinical scale of Hunt & Hess ($\geq$ 3), the greater the possibility of hormonal changes.
b) The larger the changes in tomographic studies of Fisher ($\geq$ 2), the greater the possibility of hormonal changes.
c) The location of the aneurysm in the anterior communicating artery increases the possibility of hormonal changes.
d) The presence of cerebral vasospasm is the factor most likely to cause hormonal changes.

Conclusion

The present research reveals the existence of hormonal changes of the hypothalamic-pituitary axis in SAHs by rupture of intracranial aneurysm, statistically significant for the hormones GH, TSH, free T4 and testosterone.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Ferreira M, Moreira C, Worm P. Endocrinological Changes after Subarachnoid Hemorrhage. Braz Neurosurg 2015;34(03): 179–184
2 Khajeh L, Blijdorp K, Neggers SJ, Ribbers GM, Dippel DW, van Kooten F. Hypopituitarism after subarachnoid haemorrhage, do we know enough? BMC Neurol 2014;14(01):205
3 Michils A, Balériaux D, Mockel J. Bilateral carotid aneurysms unmasked by severe hypopituitarism. Postgrad Med J 1991;67 (785):285–288
4 Hoff WV, Hornabrook RW, Marks V. Hypopituitarism associated with intracranial aneurysms. Br Med J. 1961;2(5261):1190–1194
5 Maimaitili A, Maimaitili M, Rexidan A, et al. Pituitary hormone level changes and hypxonatremia in aneurysmal subarachnoid hemorrhage. Exp Ther Med 2013;5(06):1657–1662
6 Kairys N, M. Das J, Garg M. Acute Subarachnoid Hemorrhage. 2022
7 Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci 2006;8(04):383–395
8 Edwards OM, Clark JD. Post-traumatic hypopituitarism. Six cases and a review of the literature. Medicine (Baltimore) 1986;65(05): 281–290
9 Rass V, Schoenherr E, Ianosi BA, et al. Subarachnoid Hemorrhage is Followed by Pituitary Gland Volume Loss: A Volumetric MRI Observational Study. Neurocrit Care 2020;32(02):492–501
10 Crompton MR. Hypothalamic lesions following the rupture of cerebral berry aneurysms. Brain 1963;86(02):301–314
11 Noel GL, Suh HK, Stone JG, Frantz AG. Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab 1972;35(06):840–851
12 Verbalis JG, Nelson PB, Robinson AG. Reversible panhypopituitarism caused by a suprasellar aneurysm: the contribution of mass effect to pituitary dysfunction. Neurosurgery 1982;10(05): 604–611
13 Jenkins JS, Buckell M, Carter AB, Westlake S. Hypothalamic-pituitary-adrenal function after subarachnoid haemorrhage. BMJ 1969;4(5685):707–709
14 Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C. Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 2000;93(05):743–752
15 Fernández-Real JM, Fernández-Castañer M, Villabona C, Sagarra E, Gómez-Sáez JM, Soler J. Giant intrasellar aneurysm presenting with panhypopituitarism and subarachnoid hemorrhage: case report and literature review. Clin Investig 1994; 72(04):302–306
16 Karaca Z, Hacioglu A, Kelestimur F. Neuroendocrine changes after aneurysmal subarachnoid haemorrhage. Pituitary 2019;22(03): 305–321
17 Duggan M, Browne I, Flynn C. Adrenal failure in the critically ill. Br J Anaesth 1998;81(03):468–470
18 Landon J, Greenwood FC, Stamp TC, Wynn V. The plasma sugar, free fatty acid, cortisol, and growth hormone response to insulin, and the comparison of this procedure with other tests of pituitary and adrenal function. II. In patients with hypothalamic or pituitary dysfunction or anorexia nervosa. J Clin Invest 1966;45(04): 437–449
19 Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Em: Comprehensive Physiology. Wiley; 2016:603–621
20 Krieger DT, Krieger HP. Circadian variation of the plasma 17-hydroxycorticosteroids in central nervous system disease. J Clin Endocrinol Metab 1966;26(09):929–940

21 Son YL, Ubuka T, Tsutsui K. Regulation of stress response on the hypothalamic-pituitary-gonadal axis via gonadotropin-inhibitory hormone. Front Neuroendocrinol 2022;64:100953
22 Marques P, Skorupskaite K, Rozario KS, Anderson RA, George JT. Physiology of GnRH and Gonadotropin Secretion. 2000
23 Osterman PO. Hypothalamo-pituitary-adrenal function following subarachnoid hemorrhage. Acta Neurol Scand 1975;52(01):56–62
24 Currie PJ, Khelemsky R, Rigsbee EM, et al. Ghrelin is an orexigenic peptide and elicits anxiety-like behaviors following administration into discrete regions of the hypothalamus. Behav Brain Res 2012;226(01):96–105
25 Colon G, Saccon T, Schneider A, et al. The enigmatic role of growth hormone in age-related diseases, cognition, and longevity. Geroscience 2019;41(06):759–774
26 Anjum A, Anwar H, Sohail MU, et al. The association between serum cortisol, thyroid profile, paraoxonase activity, arylesterase activity and anthropometric parameters of undergraduate students under examination stress. Eur J Inflamm 2021; 19:205873922110008
27 Mangieri P, Suzuki K, Ferreira M, Domingues L, Casulari LA. Evaluation of pituitary and thyroid hormones in patients with subarachnoid hemorrhage due to ruptured intracranial aneurysm. Arq Neuropsiquiatr 2003;61(01):14–19
28 Tsigos C, Kyrou I, Kassi E, Chrousos GP. Stress: Endocrine Physiology and Pathophysiology. 2000
29 Peters JR, Foord SM, Dieguez C, Scanlon MF. TSH neuroregulation and alterations in disease states. Clin Endocrinol Metab 1983;12 (03):669–694
30 Gupta V, Lee M. Central hypothyroidism. Indian J Endocrinol Metab 2011;15(6, Suppl 2)S99–S106
31 Cai Z, Li H. An Updated Review: Androgens and Cognitive Impairment in Older Men. Front Endocrinol (Lausanne) 2020; 11:586909
32 Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L. Menopause and cognitive impairment: A narrative review of current knowledge. World J Psychiatry 2021;11(08): 412–428
33 Qureshi AI, Suri MFK, Sung GY, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002;50(04):749–755, discussion 755–756
34 Saramma P, Menon RG, Srivastava A, Sarma PS. Hyponatremia after aneurysmal subarachnoid hemorrhage: Implications and outcomes. J Neurosci Rural Pract 2013;4(01):24–28
35 Disney L, Weir B, Grace M, Roberts P. Trends in blood pressure, osmolality and electrolytes after subarachnoid hemorrhage from aneurysms. Can J Neurol Sci 1989;16(03):299–304
36 Chandy D, Sy R, Aronow WS, Lee WN, Maguire G, Murali R. Hyponatremia and cerebrovascular spasm in aneurysmal subarachnoid hemorrhage. Neurol India 2006;54(03):273–275
37 Mapa B, Taylor BES, Appelboom G, Bruce EM, Claassen J, Connolly ES Jr. Impact of Hyponatremia on Morbidity, Mortality, and Complications After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review. World Neurosurg 2016;85:305–314
38 Tam CW, Shum HP, Yan WW. Impact of Dysnatremia and Dyskalemia on Prognosis in Patients with Aneurysmal Subarachnoid Hemorrhage: A Retrospective Study. Indian J Crit Care Med 2019; 23(12):562–567
39 Chua MMJ, Enríquez-Marulanda A, Gomez-Paz S, et al. Sodium Variability and Probability of Vasospasm in Patients with Aneurysmal Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis 2022; 31(01):106186
40 Cohen J, Delaney A, Anstey J, et al. Dysnatremia and 6-Month Functional Outcomes in Critically Ill Patients With Aneurysmal Subarachnoid Hemorrhage: A Prospective Cohort Study. Crit Care Explor 2021;3(06):e0445

Sectioning of the Filum Terminale in Patients with Chiari Malformation Type 1 Associated with Occult Tethered Cord Syndrome: Literature Review

Secção do filum terminale em pacientes com malformação de chiari tipo 1 associado a síndrome oculta da medula presa: revisão de literatura

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Abstract

Approximately 125 years ago, a group of pathologies now known as Chiari malformations was described for the first time. However, some mechanisms of its formation still remain unknown. A bibliographic survey was performed through a search in PubMed. In 1938, it was already theorized that an increase in spinal cord tension could be the cause of Chiari malformation type 1 (CM1) tonsillar herniation. In 1953, a condition known for the anchoring of the filum terminale to the vertebral canal was described for the first time and would later be known as tethered cord syndrome (TCS). Some studies have shown that it is associated with increased tension in the spinal cord, and this formed the basis for a possible pathophysiological explanation of tonsillar herniation. Case series emerged reporting that treatment for TCS with the sectioning of the filum terminale (SFT) could provide clinical improvement of patients with CM1. A new pathological entity emerged when it was realized that patients with the clinical picture of TCS could have the medullary cone in its normal position, differing from the caudal migration expected for the TCS. This condition became known as occult tethered cord syndrome (OTCS). Case series attempted to demonstrate its association with the origin of CM1, a non-intuitive association, since the cone in the normal position contradicts traction as a

Keywords
- Arnold-Chiari malformation
- cauda equina
- tonsillar herniation
- tethered cord syndrome; spinal cord

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source of tonsillar herniation. To this day, the absence of randomized control trials limits any conclusions regarding the effectiveness of SFT for the treatment of patients with CM1.

Resumo

Há cerca de 125 anos, era descrita pela primeira vez um grupo de patologias hoje conhecidas como malformações de Chiari. No entanto, alguns mecanismos de sua formação ainda permanecem desconhecidos. Um levantamento bibliográfico foi feito através do PubMed. Em 1938, já se teorizava que um aumento da tensão medular poderia ser a causa da herniação tonsilar da malformação de Chiari tipo 1 (MC1). Em 1953, foi descrita pela primeira vez uma condição conhecida pelo ancoramento do filum terminale ao canal vertebral e que mais tarde viria a ser conhecida como síndrome da medula presa (SMP). Alguns estudos demonstraram que ela estava associada à tensão aumentada na medula espinhal, e a partir disso estava formada a base para uma possível explicação fisiopatológica da herniação tonsilar. Séries de casos surgiram relatando que o tratamento para a SMP com a secção do filum terminale poderia proporcionar melhora clínica aos pacientes com MC1. Uma nova entidade patológica surgiu quando se percebeu que pacientes com o quadro clínico de SMP poderiam ter o cone medular em sua posição normal, diferente da migração caudal esperada para a SMP. Essa condição ficou conhecida como SMP oculta. Séries de casos tentaram demonstrar sua associação com a origem da MC1, uma associação nada intuitiva, visto que o cone na posição normal contradiz a tração como fonte da herniação tonsilar. A ausência de ensaios randomizados controlados até o dia de hoje não permite concluir a eficácia do método de secção do filum no tratamento de pacientes com MC1.

Palavras-chave

- Malformação de Arnold-Chiari
- Cauda Equina
- Herniação Tonsilar
- Síndrome da Medula Presa
- Medula Espinhal

Introduction

The idea that Chiari malformation (CM) could be associated with increased levels of spinal cord tension appeared around 1938, when Penfield and Coburn[1] introduced the "traction theory" to explain the formation of cerebellar herniation.

In the 1990s, studies have theorized the possibility of tethered cord syndrome (TCS) in individuals with their spinal cord in the normal position, a condition that has been called occult tethered cord syndrome (OTCS).[2]

The use of the sectioning of the filum terminale (SFT) in the treatment of patients with CM type 1 (CM1) associated with symptoms compatible with TCS and conus medullaris in the normal position is not supported by the literature. There are few published studies on this topic, and no randomized controlled trial that provides evidence of the benefit from this intervention.[3]

The present study aimed to review the published works involving patients diagnosed with CM1 and TCS with conus medullaris in the normal position who underwent SFT surgery and to highlight the impact of this procedure on the clinical picture of these patients.

Methods

A Pubmed bibliographic survey was performed. Additionally, articles were obtained through cross-reference. No time limit was established. The articles obtained ranged from historical records to the most current approaches on this topic. The descriptors used were: *Arnold Chiari malformation, type 1*, *tethered cord syndrome*, *occult tethered cord syndrome*, *filum terminale*, *sectioning of filum terminale*, and its variations, alone or in combination. For this study, articles were limited to those written in the English language in which humans were defined as the subjects.

The inclusion criteria were original articles describing the association between CM1 and OTCS and the evolution of knowledge of both pathologies and studies presenting results of the SFT in patients with CM1 and TCS with conus medullaris in the normal position (OTCS). Articles that did not report any of the correlations cited in the inclusion criteria; those that focused on other types of CM; those that exclusively addressed classical TCS, and/or duplicates between the databases were excluded. All bibliographic material included in this review was analyzed by a critical reading of the texts to assess their eligibility and to interpret and compare their findings.

Chiari Malformation Type 1

Chiari malformation comprises a group of pathologies that result from a defective formation of the rhombencephalon and posterior fossa and have cerebellar herniation in common through the foramen magnum and result from a defective formation of the rhombencephalon and posterior fossa.[4] Arnold[5] and Chiari[6] described these changes in 1894 and

1895, respectively, and some of the mechanisms involved in the formation of this disease remain unclear to this day. Chiari malformation can present in several ways and is even associated with other types of malformation, such as syringomyelia and basilar invagination. The incidence of CM1 is estimated at 1/1,000 births[7] and results from an abnormal development of the occipital bone leading to hypoplasia of the posterior fossa and tonsillar herniation.[8] If the herniation of the tonsils towards the upper medullary canal is greater than 5 mm, the condition is known as CM1.[9] This internal pressure in the spinal canal, especially in the presence of basilar invagination, which is often associated with Chiari, because it shares defects in the same anatomical region, leads to a blockage of the flow of cerebrospinal fluid (CSF) at the craniospinal junction.[10]

Treatment is directed towards patients who exhibit symptoms, and it can be done with surgical and non-surgical approaches. If the symptoms are severe, surgical intervention may be necessary. The most used technique consists of the decompression of the posterior fossa with or without duraplasty.[11–14] Other procedures used in surgical treatment in patients with CM1 are: craniectomy, meningeal repair, other brain excisions, cranial nerve decompressions, spinal decompression, fusion surgeries, and other spinal surgeries.[15]

Tethered Cord Syndrome

Tethered cord syndrome (TCS) is a widely known neurological disorder. Its concept has been developed over time among neurologists and neurosurgeons and is gaining space as a factor involved in the etiopathogenesis of other pathologies of the central nervous system. It is believed that its origin, in the congenital form, is related to defects in embryological development during secondary neurulation, leading to the infiltration of fat in the filum and a simultaneous reduction in its elasticity.[16–18] This last factor is extremely important for the development of the condition, since the filum must be elastic. The loss of this elasticity can lead to increased tension over spinal segments, resulting in the appearance of the characteristic signs and symptoms of the syndrome.[19,20] Errors in the embryological process of filum development can lead to structural changes that favor the adherence of neural tissue to adjacent structures, making it difficult for the spinal cord to rise and causing tension in the segments. This explanation for pathophysiology became known as "traction theory"[1]. The clinical findings affect the neurological, neurocutaneous, neuro-urological, and neuro-orthopedic systems.[17] The SFT surgery has been used as the standard procedure to prevent the progression of neurological signs and symptoms and to alleviate existing ones.[21–23]

Radiological Aspects

The normal filum terminale is often so thin that it can barely be detected. In the diagnosis of TCS, the thick filum terminale is often defined as greater than 2 mm in diameter.[24] This cutoff point has been cited in the literature for years and used as the upper limit of normal during intraoperative, myelographic, and magnetic resonance measurements.[25] In addition, a spinal cord that ends below the levels of the vertebral body of L2 or L3 and a conus medullaris subsequently displaced with the filum in contact with the dural sac on or near the L5 blade have been established to aid in the diagnosis of this condition.[26,27] Fat appears as low attenuation on computed tomography (CT) and brilliant in T1-weighted magnetic resonance imaging (MRI) sequences.[28] However, a fatty filum can be an incidental finding,[29,30] and it is not considered a diagnosis of TCS, as it is present in 5.8% of the normal population in the postmortem examination.

The Traction Theory

The idea that CM could be associated with increased levels of spinal cord tension appeared around 1938, when Penfield and Coburn[1] introduced the *traction theory* to explain the formation of cerebellar herniation. This theory is based on the observation of CM1 in children with some condition that causes the adhesion of lower segments of the spinal cord to the spinal canal, such as myelomeningocele, which, due to the uneven development rate between the spinal canal and the spinal cord would lead to an increase in the lowering tension in the spinal cord and consequently cerebellar displacement through the foramen magnum. However, several studies have reported cases of patients who developed CM1 as an adult or in children who did not have any condition that would lead to spinal cord anchorage.[31–34] In addition, Barry et al.[35] studied fetuses and babies with lumbosacral myelomeningocele and concluded that there is a degree of tension resulting from the anchoring of the spinal cord caused by this condition. However, they stated that they do not believe that this tension extends to the upper portion of the spinal cord, having more influence on the portions close to the adhesion site, which would make the theory of traction improbable as a cause of tonsillar herniation. Even so, there is no study that evaluates spinal cord traction in vivo alone since the studies contain other variables that may function as a potential mechanism of tonsillar herniation, such as hydrocephalus, myelomeningocele, caudal displacement of the brainstem and cerebellum, hypoplasia of the posterior fossa of the skull, and enlargement of the foramen magnum.[36,37] In an experimental study using a fresh cadaveric model, Tubbs et al.[38] observed the movements of the spinal cord, brain stem, and cerebellar tonsils after applying tension to the conus medullaris. As a result, there was less than 1 mm of movement in the caudal portion of the brainstem and cervical spinal cord and no change in the position of the cerebellar tonsils, suggesting that the SFT is an unlikely method of reversing tonsillar herniation in cases of CM1.

Occult Tethered Cord Syndrome and Chiari Malformation Type 1

In the 1990s, studies theorized the possibility of TCS in individuals with the spinal cord in the normal position. These patients would have the clinical characteristics of a patient with TCS associated with a conus in the normal

position and a filum with structural changes in the MRI. The occurrence of this condition was first proposed by Warder and Oakes[2] in 1993, and, after that, several case series of surgical intervention were published with consequent clinical improvements in patients with this condition, which came to be called occult spinal cord syndrome.[17,39–43] However, with the cone in the normal position, the etiology of this condition began to be questioned since the theory of spinal cord traction assumed that due to a spinal cord attached through its filum terminale, there was a downward movement of the spinal cord. In their work, Milhorat et al.[36] provided data that would support the hypothesis of a tethered spinal cord even in patients with a cone in the normal position. In this study, it was observed that the filum terminale's width decreased steadily during growth and development, with most patients with a normal spinal cone position presenting positive filament traction tests at the time of surgery. Immediately after the SFT, there was a marked distraction of the divided extremities, in addition to improvement in the regional flow of the CSF.

Yet, based on the previously mentioned findings, the question arises as to how traction would act in the formation of cerebellar herniation in a patient in which the conus medullaris is in the normal position. Some studies have presented a series of cases reporting the outcome in patients with OTCS and tonsillar herniation who underwent SFT (►**Table 1**).

Main Studies on SFT in Patients with CM1 and OTCS

Royo-Salvador et al.[44] evaluated 20 patients who underwent their service between 1993 and 2003, among whom 8 had only scoliosis, 5 only syringomyelia, 2 only CM1, and 5 with a combination of these. Among the five mentioned, two had CM1 among their pathologies, totaling four patients with CM1. All were symptomatic and underwent SFT. Age ranged from 14 to 51 years old. In all patients, signs and symptoms disappeared or spontaneously improved after SFT. Three of the four with CM1 considered the surgery to be helpful, and the fourth patient's opinion was unknown. The author states that the improvement in symptoms in these patients must be associated with the disappearance of tension on the spinal cord after surgery. However, he admits that animal experiments have failed to produce CM1 by pulling the filum down. Recently, a systematic review[3] that included this study concluded that it has low methodological quality, and it is not possible to indicate SFT as a treatment for CM1, being, therefore, considered an experimental treatment.

Yuan Zhou et al.[45] published a case of a 14-year-old child admitted with intermittent pain and numbness in his right upper limb. He also had increased urinary frequency, pain in the neck and in the spine. Imaging exams revealed CM1 and syringomyelia and a medullary cone at the level of L1, a clinical and imaging diagnosis compatible with OTCS. He underwent SFT and had pain relief, improvement in the urodynamic test and urinary dysfunction, but there was no change in the position of the conus medullaris. After 1 year, he was readmitted with numbness in his right upper limb and right side of his back and occasionally pain in his waist. He performed posterior fossa decompression and evolved in the postoperative period with retraction of the cerebellar tonsils and 6 months later with improvement of symptoms. The cone remained in the normal position.

Glenn et al.[4] reported 17 cases (mean age 7.0 years) of CM1 associated with TCS in which they underwent SFT. Of these, 8 had the conus medullaris ending up to the lower portion of L2. The most common symptoms were headache and sensory disturbances of the lower extremities. Many of them were initially referred for posterior fossa decompression; however, due to a condition incompatible with classical CM1, further investigation was carried out. After SFT, 16 patients had the level of tonsillar herniation unchanged, and one had a rise in the cerebellar tonsils. According to the authors, all patients had some level of neurological improvement, and no worsening was detected. Therefore, they suggest that patients with CM1 and TCS who do not demonstrate classic symptoms of CM1 may benefit from SFT. The study does not specify how the clinical improvement of these patients was measured and does not correlate the level of improvement with the position of the conus medullaris, which makes it difficult to conclude whether there is a relationship between the clinical improvement and SFT in patients with CM1 associated with the conus medullaris in the normal position.

Selcuki et al.[46] presented 7 patients diagnosed with CM1 and TCS and who underwent SFT. As a diagnostic criterion for CM1, the clinical and radiological findings of tonsillar herniation were used, and for TCS, the clinical findings and the position of the conus medullaris below L2 and a fatty or thickened filum were used. Patients who had the conus in the normal position were referred for evaluation using the spinal somatosensory evoked potential (SSEP).T who had delayed or blocked nerve conduction were considered compatible with the diagnosis of TCS and underwent SFT before an approach to tonsillar herniation. All seven patients had CM1 and symptoms of TCS associated with a conus medullaris in a normal position and all underwent surgery. In the postoperative follow-up, there was no change in tonsillar herniation. On the other hand, there was a significant improvement in the symptoms of TCS and CM1, which leaves open the question of the contribution of tonsillar herniation alone to the symptoms in CM1.

Abel et al.[47] reported the case of a 3-year-old child with progressive imbalance and torticollis, in addition to anomalies compatible with Klippel-Feil syndrome and progressive scoliosis since birth. The CT showed the fusion of cervical vertebrae. Medical history also revealed a cleft palate and an extra-numerical finger in the hand, both surgically corrected, in addition to developmental delay. There were no changes in bladder or bowel function. A comparison of MRI images differing in three years revealed that CM1 signs were identified in the second MRI that were not identifiable in the first, suggesting that the pathology was not congenital, but acquired throughout life. In the MRI, fatty filum and conus medullaris were identified ending at the level of L2. The

Table 1 Patients with CM1 and TCS with conus medullaris in normal position who underwent SFT

	AGE/SEX	DIAGNOSIS	CMD	OUTCOME	POST OP MRI	FOLLOW-UP
Royo-Salvador et al., 2005[44]	Age range: 20–67 years; mean age: 38 years; sex: F (2) M (2)	CM1 (2)* CM1 + syringomyelia + scoliosis (2)**	L1-L2	40–100% of improvement	Rise of CMD (1)	4–11 years
Abel et al., 2006[47]	F, 3 years.	CM1 + fatty FT + Klippel- Feil Syndrome.	L2	Improvement of imbalance and stiff neck; Klippel- Feil and scoliosis stable;	CM1 and CMD unchanged	15 months
Milhorat et al., 2009[36]	CM1 + TCS: 31.5 ± 12.4 years LLCT + TCS: 31.0 ± 12.5 years 318 total (74 children, 244 adults)	CM1 (TH >= 8 mm) or LLCT (TH 0–7 mm) + TCS with NLCM	Above L2 in 60 (81%) children and 240 (98%) adults	Signs and symptoms: complete resolution in 27 (36%) children and 44 (18%) adults and improvement in 42 (57%) children and 159 (65%) adults.	Complete improvement or reduction of syringes in 76 (55%) of 138 patients; Complete resolution or improvement of scoliosis in 27 (38%) of 71 patients.	Children: mean of 14.8 ± 4.38 months Adults: mean of 16.5 ± 5.04 months
Glenn et al., 2015[4]	Mean age: 7 years	CM1 (17) TH mean of 10 mm	L1 (1) L1–2 (5) L2 (2) L2–3 (7) L3 (2)	100% had some level of improvement	TH unchanged (16) TH reduction (1)	Mean of 21.3 months
Selcuki et al., 2016[46]	Age range: 14-51 years; mean age: 30.7 years; sex: F (5) M (2)	Only CM1 (3) CM1 + syringomyelia (4)	Normal position	60–100% of improvement	TH unchanged	6–33 months
Zhou et al., 2017[45]	14, M	CM1 + Syringomyelia	L1	Clinical and image improvement	CM1 resolution, 6 months after surgery	2 years

Abbreviations: CM1, Chiari malformation type 1; CMD, conus medullaris; F, female; FT, filum terminale; LLCT, low-lying cerebellar tonsils; M, male; MRI, magnetic resonance imaging; NLCM, normal level *conus medullaris*; SFT, sectioning of the filum terminale; TCS, tethered cord syndrome; TH, tonsillar herniation.

*(cases 4 and 11 in the study)

** (cases 5 and 16 in the study)

authors mention that during SFT, a high-tension filum was observed by the surgeon, which was relieved after the sectioning. In the 15-month follow-up, the child showed improvement in his imbalance and torticollis and the other changes remained stable. Postoperative MRI showed no change in CM1 or in the position of the conus medullaris. The parameters used to assess clinical improvement were not mentioned. Milhorat et al.[36] in their retrospective study gathered a large cohort of 2,987 patients with CM1 (defined as tonsillar herniation greater than or equal to 5 mm below the FM) and 289 patients with small tonsillar herniation (LLCT - defined as tonsillar herniation between 0 and 4 mm below the FM) between January 2002 and July 2007. Tethered cord syndrome was present in 14% of the patients with CM1 and 63% of the patients with LLCT, which, according to the authors, reveals an association between these diseases. Of the total patients in the sample, 46% were referred due to previous surgical failure to treat CM1. Among the patients who had CM1 and TCS or LLCT and TCS, 318 underwent SFT. Among these, the age ranged from 12 months to 60 years (mean $\pm$ SD: 29.5 ± 4.1 years) and were divided into 2 groups —children (between 0–18 years old) and adults (18 years old or older). Previous surgical failure for CM1 was observed in 26% of children and 55% of adults. The authors mention that after CM1 surgery, the patients improved for several months, but the symptoms returned or worsened after that period and many had to undergo a second procedure, such as a review of posterior fossa decompression, cranioplasty, and a CSF shunt. These previous interventions can influence patients' response to SFT, and it is not possible to attribute the results only to the sectioning of the filum. All of them underwent a complete physical and neurological examination and a series of imaging tests. The diagnosis of TCS was made based on clinical and radiological criteria and included patients with a medullary cone ending below (19% of children and 7% of adults) and above (81% of children and 98% of adults) the lower edge of L2, with a statistically significant difference between adults and children in both cases. The postsurgical result was followed by a period ranging from 6 to 27 months (16.1 ± 4.6 months). A complete resolution of symptoms occurred more frequently in children than in adults (36% compared to 18%, $p < 0.001$, respectively), improved in 57% of children and 65% of adults, did not change in 7% of children and in 16% of adults, and worsened in 1% of adults. According to the authors, the low rate of complete symptom resolution was due to herniations of the rhombencephalon, the presence of syringomyelia, scoliosis, and interference from previous surgical treatments. Cranial migration of the conus medullaris was detected at an average distance of 5.1 mm ($p < 0.001$), being greater in children than in adults, in addition to a reduction in tonsillar herniation (average of 3.8 mm, $p < 0.001$) and a reduction in distance of the fourth ventricle below the Twining line (average of 2.6 mm, $p < 0.01$). The increase in medullary height, the reduction of tonsillar herniation, and the distance from the fourth ventricle to the Twining line was taken as evidence of cranial migration of the brainstem and cerebellum. The authors mentioned that after SFT of these patients, it was possible to notice a rapid removal of the ends of the filum, suggesting that they were under strong traction, and, through the transdural Doppler ultrasound, it was possible to detect a statistically significant increase in the CSF flow speed.

Conclusion

The evaluation of the benefits of SFT for the correction of the symptoms of CM1 is extremely difficult, since to date it is supported only by observational studies. These studies also have important limitations, which include: a lack of objective parameters for improvement, a relatively short follow-up in most of the studies, a lack of homogeneity in the samples (patients with several other pathologies and previous surgeries) that may interfere with the surgical results, and the absence of a clear correlation between the clinical improvements reported in the studies and the patients' anatomy, which often did not change. Nevertheless, these studies are important milestones of these pathologies. Basic science studies looking for associated molecular mechanisms and randomized controlled clinical trials are needed for further understanding.

Contribution Details
Acquisition of data: J.N.P.O.B., P.A.D., P.B.B.J.,
Analysis and interpretation of data: J.N.P.O.B., P.A.D., P.B.B.J.
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Conflict of Interests
The authors have no conflict of interests to declare.

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References

1 Penfield W, Coburn DF. Arnold-Chiari malformation and its operative treatment. Arch NeurPsych. 1938;40(02):328–336
2 Warder DE, Oakes WJ. Tethered cord syndrome and the conus in a normal position. Neurosurgery 1993;33(03):374–378
3 Milano JB, Barcelos ACES, Daniel JW, et al. Chiari malformation Type I - effect of the section of the filum terminale. Rev Assoc Med Bras 2020;66(08):1021–1025
4 Glenn C, Cheema AA, Safavi-Abbasi S, Gross NL, Martin MD, Mapstone TB. Spinal cord detethering in children with tethered cord syndrome and Chiari type 1 malformations. J Clin Neurosci 2015;22(11):1749–1752
5 Arnold J. Myelocyste, Transposition von Gewebskeimen und Sympodie. Zieglers Beitr Pathol Anal. 1894;16:1–28
6 Chiari H. Uber Veranderungen des Kleinhirns, des Pons und der Medulla Oblongata infolge von congenitaler Hydrocephalie des Grosshirns. Denksehriften der Kais Akad Wiss math-naturw 1896;63:71–116

7 Alkoç OA, Songur A, Eser O, et al. Stereological and Morphometric Analysis of MRI Chiari Malformation Type-1. J Korean Neurosurg Soc 2015;58(05):454–461
Ferreira JA, Botelho RV. The odontoid process invagination in normal subjects, Chiari malformation and Basilar invagination patients: Pathophysiologic correlations with angular craniometry. Surg Neurol Int 2015;6:118

9 Brito JNPO, Santos BAD, Nascimento IF, Martins LA, Tavares CB. Basilar invagination associated with chiari malformation type I: A literature review. Clinics (São Paulo) 2019;74:e653

10 Brito JNPO, Klawki P, Schwarz M, Voth D. Late result in cases of atlanto-axial dislocations after dosal fusion. In: Voth D, Gless P, eds. Diseases in the cranio-cervical junction. Berlin: De Gruyter; 1987:279–86

11 Akar E, Kara S, Akdemir H, Kırış A 3D structural complexity analysis of cerebellum in Chiari malformation type I. Med Biol Eng Comput 2017;55(12):2169–2182

12 McGirt MJ, Attenello FJ, Atiba A, et al. Symptom recurrence after suboccipital decompression for pediatric Chiari I malformation: analysis of 256 consecutive cases. Childs Nerv Syst 2008;24(11): 1333–1339

13 Shoja MM, Johal J, Oakes WJ, Tubbs RS. Embryology and pathophysiology of the Chiari I and II malformations: A comprehensive review. Clin Anat 2018;31(02):202–215

14 Kalb S, Perez-Orribo L, Mahan M, Theodore N, Nakaji P, Bristol RE. Evaluation of operative procedures for symptomatic outcome after decompression surgery for Chiari type I malformation. J Clin Neurosci 2012;19(09):1268–1272

15 Passias PG, Pyne A, Horn SR, et al. Developments in the treatment of Chiari type 1 malformations over the past decade. J Spine Surg 2018;4(01):45–54

16 Lew SM, Kothbauer KF. Tethered cord syndrome: an updated review. Pediatr Neurosurg 2007;43(03):236–248

17 Selçuki M, Vatansever S, Inan S, Erdemli E, Bağdatoğlu C, Polat A. Is a filum terminale with a normal appearance really normal? Childs Nerv Syst 2003;19(01):3–10

18 Hertzler DA II, DePowell JJ, Stevenson CB, Mangano FT. Tethered cord syndrome: a review of the literature from embryology to adult presentation. Neurosurg Focus 2010;29(01):E1

19 Selçuki M, Coşkun K. Management of tight filum terminale syndrome with special emphasis on normal level conus medullaris (NLCM). Surg Neurol 1998;50(04):318–322, discussion 322

20 Selcuki M, Mete M, Barutcuoglu M, Duransoy YK, Umur AS, Selcuki D. Tethered Cord Syndrome in Adults: Experience of 56 Patients. Turk Neurosurg 2015;25(06):922–929

21 Yamada S, Won DJ, Yamada SM. Pathophysiology of tethered cord syndrome: correlation with symptomatology. Neurosurg Focus 2004;16(02):E6

22 Tani S, Yamada S, Knighton RS. Extensibility of the lumbar and sacral cord. Pathophysiology of the tethered spinal cord in cats. J Neurosurg 1987;66(01):116–123

23 Yamada S, Zinke DE, Sanders D. Pathophysiology of "tethered cord syndrome". J Neurosurg 1981;54(04):494–503

24 Saker E, Henry BM, Tomaszewski KA, et al. The filum terminale internum and externum: A comprehensive review. J Clin Neurosci 2017;40:6–13

25 Yundt KD, Park TS, Kaufman BA. Normal diameter of filum terminale in children: in vivo measurement. Pediatr Neurosurg 1997;27(05):257–259

26 Cramer G, Darby S. Basic and clinical anatomy of the spine, spinal cord, and ANS. 2nd ed. St. Louis: Elsevier Mosby; 2005

27 Pinto FCG, Fontes Rde V, Leonhardt Mde C, Amodio DT, Porro FF, Machado J. Anatomic study of the filum terminale and its correlations with the tethered cord syndrome. Neurosurgery 2002;51 (03):725–729, discussion 729–730

28 Hinshaw DB Jr, Jacobson JP, Hwang J, Kido DK. Imaging of Tethered Spinal Cord. In: Yamada S, ed. Tethered cord syndrome in children and adults. New York: AANS; 1996:51–64

29 McLendon RE, Oakes WJ, Heinz ER, Yeates AE, Burger PC. Adipose tissue in the filum terminale: a computed tomographic finding that may indicate tethering of the spinal cord. Neurosurgery 1988;22(05):873–876

30 Rizk E, Adeeb N, Hussein AE, Tubbs RS, Rozzelle CJ, Oakes WJ. Duplicated filum terminale in the absence of split cord malformation: a potential cause of failed detethering procedures. Childs Nerv Syst 2014;30(04):709–711

31 Adams RD, Schatzki R, Scoville WB. The Arnold–Chiari Malformation. N Engl J Med 1941;225(04):125–131

32 McConnell AA, Parker HL. A deformity of the hind-brain associated with internal hydrocephalus. Its relation to the Arnold-Chiari malformation. Brain 1938;61(04):415–429

33 Ogryzlo MA. The Arnold-Chiari malformation. Arch NeurPsych. 1942;48(01):30–46

34 Swanson HS, Fincher EF. Arnold-Chiari deformity without bony anomalies. J Neurosurg 1949;6(04):314–319

35 Barry A, Patten BM, Stewart BH. Possible factors in the development of the Arnold-Chiari malformation. J Neurosurg 1957;14 (03):285–301

36 Milhorat TH, Bolognese PA, Nishikawa M, et al. Association of Chiari malformation type I and tethered cord syndrome: preliminary results of sectioning filum terminale. Surg Neurol 2009;72 (01):20–35

37 Di Rocco C, Rende M. Neural tube defects. Some remarks on the possible role of glycosaminoglycans in the genesis of the dysraphic state, the anomaly in the configuration of the posterior cranial fossa, and hydrocephalus. Childs Nerv Syst 1987;3(06): 334–341

38 Tubbs RS, Loukas M, Shoja MM, Oakes WJ. Observations at the craniocervical junction with simultaneous caudal traction of the spinal cord. Childs Nerv Syst 2007;23(04):367–369

39 Metcalfe PD, Luerssen TG, King SJ, et al. Treatment of the occult tethered spinal cord for neuropathic bladder: results of sectioning the filum terminale. J Urol 2006;176(4 Pt 2):1826–1829, discussion 1830

40 Nazar GB, Casale AJ, Roberts JG, Linden RD. Occult filum terminale syndrome. Pediatr Neurosurg 1995;23(05):228–235

41 Selçuki M, Unlü A, Uğur HC, Soygür T, Arikan N, Selçuki D. Patients with urinary incontinence often benefit from surgical detethering of tight filum terminale. Childs Nerv Syst 2000;16(03):150–154, discussion 155

42 Selden NR, Nixon RR, Skoog SR, Lashley DB. Minimal tethered cord syndrome associated with thickening of the terminal filum. J Neurosurg 2006;105(03):214–218

43 Wehby MC, O'Hollaren PS, Abtin K, Hume JL, Richards BJ. Occult tight filum terminale syndrome: results of surgical untethering. Pediatr Neurosurg 2004;40(02):51–57, discussion 58

44 Royo-Salvador MB, Solé-Llenas J, Doménech JM, González-Adrio R. Results of the section of the filum terminale in 20 patients with syringomyelia, scoliosis and Chiari malformation. Acta Neurochir (Wien) 2005;147(05):515–523, discussion 523

45 Zhou Y, Zhu L, Lin Y, Cheng H. Chiari type I malformation with occult tethered cord syndrome in a child: A case report. Medicine (Baltimore) 2017;96(40):e8239

46 Selcuki M, Mete M, Selcuki D. Are Herniated Cerebellar Tonsils the Main Culprit of Chiari Malformation Type I Symptoms? The Brainstem Compression Hypothesis seems to be Re-Elucidated and Revised. Turk Neurosurg 2018;28(01):67–71

47 Abel TJ, Chowdhary A, Gabikian P, Ellenbogen RG, Avellino AM. Acquired chiari malformation type I associated with a fatty terminal filum. Case report. J Neurosurg 2006;105(04, Suppl)329–332

Brain Metastasis is Associated with Tumor Size, Nodal Status, and c-erbB-2 Expression in Invasive Breast Carcinoma

A metástase cerebral está associada com tamanho tumoral, status nodal e expressão de c-erbB-2 no carcinoma invasivo de mama

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Abstract

Introduction According to the World Health Organization (WHO) classification, invasive breast carcinoma (IBC) of no special type (IBC-NST) is the second most common primary site of central nervous system metastases, affecting 15% to 30% of patients. Brain metastasis originating from IBC is associated with patient age, tumor size, and axillary lymph node status. Loss of expression of hormone receptors and c-erbB-2 amplification are frequent findings in patients who develop brain metastasis. Radiological studies of the central nervous system are carried out only in patients presenting with neurological signs or symptoms during the clinical follow-up.

Objective To evaluate the associations of clinical and pathological findings with brain metastasis in breast cancer.

Materials and Methods The sample comprised 73 patients with breast cancer who underwent mastectomy with lymph node resection. The following variables were evaluated: tumor size, histological grade, nodal state, expression of estrogen and progesterone receptors and c-erbB-2, and presence of brain metastasis.

Results The histopathological findings associated with brain metastasis in patients with IBC were tumor size ($p = 0.03$), presence of nodal metastasis ($p = 0.045$), and c-erbB-2 expression ($p = 0.012$).

Conclusion The assessment of specific pathological findings in breast carcinoma can help identify risk factors and/or clinical parameters associated with the development of brain metastasis.

Keywords
- central nervous system
- carcinoma
- breast
- tumor metastasis
- pathology
- prognosis

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Resumo

Introdução O carcinoma invasivo de mama (CIM) de tipo não especial, segundo a classificação da Organização Mundial de Saúde, é o segundo sítio primário mais comum de metástases do sistema nervoso central, afetando de 15% a 30% das pacientes. A metástase cerebral originada de CIM está associada à idade do paciente, tamanho do tumor, estado nodal axilar e perfil imuno-histoquímico do local primário. A perda da expressão dos receptores hormonais e a amplificação do c-erbB-2 são achados frequentes em pacientes que desenvolvem metástase cerebral. Estudos radiológicos do sistema nervoso central são realizados apenas em pacientes que apresentam sinais ou sintomas neurológicos durante o acompanhamento clínico.

Objetivo Este estudo teve como objetivo avaliar associações de achados clínicos e patológicos com metástase cerebral em IBC. Método: A amostra foi composta por 73 pacientes com CIM submetidas à mastectomia e ressecção nodal axilar. Foram avaliadas as seguintes variáveis: tamanho do tumor, grau histológico, estado nodal, expressão de receptores de estrogênio e progesterona e c-erbB-2 e presença de metástase cerebral tratada por ressecção cirúrgica.

Resultados Os achados histopatológicos associados à metástase cerebral em pacientes com IBC foram tamanho do tumor ($p = 0,03$), presença de metástase nodal ($p = 0,045$) e expressão de c-erbB-2 ($p = 0,012$).

Conclusão A avaliação de achados patológicos específicos no IBC pode ajudar a identificar fatores de risco e/ou parâmetros clínicos associados ao desenvolvimento de metástase cerebral.

Palavras-chave

- sistema nervoso central
- carcinoma
- seios
- metástase tumoral
- patologia
- prognóstico

Introduction

According to the World Health Organization (WHO) classification, invasive breast carcinoma (IBC) of no special type (IBC-NST) is a heterogeneous malignant neoplasm characterized by extensive histopathological, genetic, and immunohistochemical alterations.[1–4] It represents the second most common primary site of central nervous system (CNS) metastases, affecting 15% to 30% of the patients. The occurrence of brain metastasis in patients with IBC is associated with age, tumor size, axillary lymph node status, and immunohistochemical profile of the primary tumor site.[2,4–6] Loss of expression of hormone receptors and amplification of human epidermal growth factor receptor-2 (HER-2) are frequent findings in patients who develop brain metastasis. Radiological examination of the CNS is carried out only in patients presenting with neurological signs or symptoms during the clinical follow-up.[1,3,4,6,7]

In the present study, the authors investigated anatomopathological variables that could be associated to the development of CNS metastasis in patients with IBC-NST.

Materials and Methods

The present cross-sectional study analyzed 73 cases of IBC-NST registered at the Pathology Laboratory of Hospital Nossa Senhora da Conceição, in the city of Porto Alegre, Southern Brazil, between May 2003 and April 2020. Specimens from total mastectomy with axillary lymph node resection were fixed in 10% buffered formalin, embedded in paraffin, stained with hematoxylin and eosin, and analyzed for estrogen receptor, progesterone receptor, c-erbB-2 (HER2), and Ki-67 expression using an automated immunohistochemical method (Ventana HE 600 System, Roche Diagnostics, Basel, Switzerland). The WHO histopathological criteria for IBC were used for tumor diagnosis and to determine the histological grades. The cases of IBC were graded according to the Nottingham classification system, which categorizes tumors into three stages of differentiation (1 to 3) according to patterns of tubule formation, nuclear pleomorphism, and mitotic index. The tumor-node-metastasis (TNM) system of tumor classification was used for clinical and pathological staging.

All patients with IBC and brain metastasis underwent surgical resection or tissue biopsy due to neurological signs and/or deficits. Patients with brain metastasis had positive immunoexpression for cytokeratin 7 (CK7), epithelial membrane antigen (EMA), mammaglobin, gross cystic disease fluid protein 15 (GCDFP-15), and T-cell specific transcription factor GATA-3, as well as negative immunoexpression for cytokeratin 20 (CK20), intestinal transcription factor CDX-2, thyroid transcription factor 1 (TTF-1), napsin, paired box transcription factor 8 (PAX-8), renal cell carcinoma-associated antigen (RCC), and carbohydrate antigen 19-9 (CA19-9).

The exclusion criteria were as follows: men with IBC, history of breast cancer, patients with breast cancer who had only undergone biopsy or breast sectorectomy, patients without immunohistochemical evaluation of the primary site or without histopathological evaluation of the metastatic brain lesion, other histological types of breast neoplasms, brain metastases associated with other primary sites, previous therapies for the current breast carcinoma (chemotherapy,

radiotherapy and/or hormonal therapy), and patients without clinical follow-up for at least 24 months.

The analyzed variables were patient age, tumor size (primary lesion), tumor grade, multifocality/multicentricity (primary lesion), presence of nodal or brain metastases, presence of intraductal lesions, expression for estrogen receptors, progesterone receptors, c-erbB-2, and Ki-67 (primary lesion), topography of brain metastases, size of and number of metastatic brain lesions, disease-free survival time, and clinical outcome (death, progression, or tumor recurrence in the breast parenchyma).

Quantitative variables were expressed as mean and standard deviation or median and interquartile range values. Categorical variables were reported as absolute and relative frequencies. The Student *t*-test was used to compare means between groups. The Mann–Whitney test was used for variables with skewed distribution. Comparisons regarding proportions were performed using the Pearson Chi-squared test and the Fisher exact test. Poisson regression was used to control confounding factors. Variables significant at $p < 0.2$ in the bivariate model were included in the multivariate model. The significance level was set at $p \leq 0.05$. The analyses were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, US) software, version 20.0.

Results

The mean age of the 73 patients in the sample was of 50.42 (± 7.565) years. The mean tumor size was of 2.48 (± 1.224) cm, with a mean of 18.6 (± 3.257) lymph nodes isolated in each specimen. Patients in the group without brain metastasis ($n = 51$) were predominantly classified as T1 (n = 20; 39.2%) N1 (n = 16; 50%) in the TNM staging system. Patients that developed brain metastasis ($n = 22$) were predominantly classified as T2 (n = 14; 63.6%) N2 (n = 7; 50%) according to the TNM. ►**Tables 1**, **2**, and the ►**Appendix** show the results of the present study. The histopathological findings associated with the presence of brain metastasis in patients with IBC were tumor size ($p = 0.03$), presence of nodal metastasis ($p = 0.045$), and c-erbB-2 expression ($p = 0.012$). The median time between the anatomopathological diagnosis of the primary tumor and the diagnosis of brain metastasis was of 29.5 months. The mean age did not differ between patients with and without brain metastasis. Triple-negative breast cancers were more frequent in the brain-metastasis group, with 4 cases among the 22 analyzed (19.04%). The prevalence of triple-negative tumors was of 8% ($n = 4$) among patients who did not have brain metastasis.

The brain-metastasis group had a survival probability of 11% after 120 months, whereas the group without brain

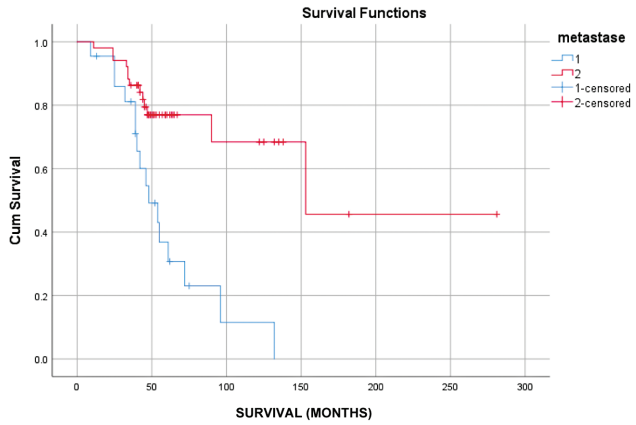

Fig. 1 Survival index associated to brain metastases in invasive breast carcinoma.

Table 1 Invasive breast cancer and central nervous system metastasis: relationships regarding age, histologic grade, and lymph node metastasis

Variable	Group without brain metastasis ($n = 51$)	Group with brain metastasis ($n = 22$)	*p*-value
Age, years	51.71 ± 12.727	49.32 ± 13.891	0.478
Histologic grade, *n* (%)			
1	5 (9.8%)	0 (0%)	0.308
2	26 (51%)	13 (59.1%)	
3	20 (39.2%)	9 (40.9%)	
Lymph node metastasis, *n* (%)			
Yes	32 (62.7%)	8 (36.4%)	0.045
No	19 (37.3%)	14 (63.6%)	
Size			
T1	20 (39.2%)	3 (13.6%)	0.03
T2	16 (31.4%)	14 (63.6%)	
T3	15 (29.4%)	5 (22.7%)	

Table 2 Invasive breast cancer and central nervous system metastasis: comparison of hormone receptor and HER-2 expression between groups

Variable	Group without brain metastasis ($n = 51$)	Group with brain metastasis ($n = 22$)	*p*-value
Estrogen receptors			
Negative	13 (25%)	11 (50%)	0.058
Positive	38 (75%)	11 (50%)	
Progesterone receptors			
Negative	18 (35.3%)	13 (59.1%)	0.074
Positive	33 (64.7%)	9 (40.9%)	
Human epidermal growth factor receptor-2 (HER-2)			
Negative	40 (78.4%)	10 (45.5%)	0.012
Positive	11 (21.6%)	12 (54.5%)	
Luminal A	11 (21.6%)	2 (9.1%)	0.019
Luminal B	19 (37.3%)	4 (18.2%)	

(*Continued*)

metastasis had a 68% chance of survival. The mean time until the presentation of brain metastasis was of 50 months after mastectomy (►**Fig. 1**). At this time, the relative risk of death was 3.8 times higher in the brain-metastasis group.

Discussion

The incidence of brain metastasis associated with IBC has increased in recent years. Although early detection of the primary lesion and different modalities of clinico-surgical treatment have consistently contributed to an increase in disease-free survival time, some patients manifest an aggressive biological course and develop brain, liver, or bone metastases.[1–3,5] In general, most chemotherapeutic agents, hormone therapies, and/or other target therapies present regular or poor effectiveness in patients with brain metastasis because these agents do not efficiently penetrate the blood–brain barrier. Important advances were obtained with the introduction of trastuzumab for the control of systemic diseases, but with little effect in patients with brain metastasis.[2,3,5,6,8,9] Currently, surgical resection, radiotherapy, and/or stereotactic radiosurgery are the most effective therapeutic measures for severe or acute neurological conditions, particularly in patients with neurological complaints.[2–4,6,9,10] The determination of anatomopathological factors capable of predicting the risk of brain metastasis in IBC patients may contribute to the increase in survival rates and identification of possible molecular pathways for pharmacological control. The current survival time of patients with brain metastasis ranges from 3 to 8 months.[1,2,4,5,7,9–11]

In general, young age, low disease-free interval, visceral metastasis, positive immunoexpression for c-erbB-2, and high number of metastatic sites are associated with the development of brain metastasis in IBC.[2,3,5,6,8,12–14] We found a higher ($p = 0.004$) incidence of brain metastasis in patients with positive expression for c-erbB-2. Brufsky et al.[5] found a cumulative incidence of brain metastasis of 31% over a 2-year period. Montagna et al.,[9] in a cohort of patients with newly diagnosed c-erbB-2-positive IBC, detected the presence of brain metastasis through computed tomography (CT) in about 6% of the patients at the time of initial diagnosis of the primary lesion, and in 40% of the sample at a median follow-up of 35.3 months.

Pellerino et al.[10] reported the presence of brain metastasis in 8% to 15% of advanced luminal A IBC cases, 11% of luminal B IBC cases, 11% to 48% of HER-2-positive carcinoma cases, and 25% to 46% of triple-negative cases. Yan et al.[15] analyzed 295 subjects with IBC using CT or magnetic resonance imaging (MRI) and detected brain metastasis in 49 patients (17%) in an interval of 6 months. In their study,[15] molecular subtype was associated with brain metastasis development over 12 months: 3.3% of the cases were luminal A, 14% were luminal B, 38% were c-erbB-2-positive, and 18% were triple-negative. The low incidence of brain metastasis as the first site of disease spread in patients with IBC (0.1% to 3.2% per year of follow-up) is considered by some authors a relevant factor for not conducting routine radiological investigation, even in patients with c-erbB-2 expression, triple-negative carcinomas, and locally advanced tumors. The patients in the current study had a median time of 29.5 months between diagnosis of the primary tumor and diagnosis of brain metastasis. Niwińska et al.[8] identified asymptomatic brain metastasis in 11 out of 32 women (34%) with c-erbB-2-positive IBC 3 to 84 months after the initial diagnosis (median of 15 months) using a single MRI scan.

For patients with c-erbB-2-positive IBC who developed regional or distant metastases and/or patients with triple-negative IBC, the 1-year cumulative incidence of brain metastasis ranges from 10% to 30%, which may support the need for radiological screening even in asymptomatic cases.[1,2,5,8,9,15,16] Because of the significant morbidity and mortality rates associated with brain metastasis in IBC, it is suggested that routine radiological assessments be carried out in high-risk populations.[2,5,8,9,16–18] According to Kuksis et al.,[13] clinical trials, such as the MRI Screening Versus SYMptom-directed Surveillance for Brain Metastases Among Patients with Triple Negative or HER2$^+$ MBC (SYMPToM, NCT03881605), are currently underway to investigate the potential risks and benefits of early detection and intervention of brain metastasis.

In recent years, there has been an increasing emphasis on molecular prognostic tests to the detriment of traditional clinical and pathological methods. Nevertheless, the number of regional lymph nodes affected by metastasis, the histological grade, and tumor size remain essential for prognosis and therapeutic decision-making.[3,5,9,14–16,19–21] According to Carter et al.,[22] the probability of developing metastasis increases with increasing tumor size. Patients with T1 tumors had a 100% 5-year overall survival, whereas patients with T2 and T3 had 89% and 86% survival rates respectively. Fung et al.[23] argued that tumor size (≤ 2 cm versus > 2 cm) and lymph node status are independent prognostic factors for local recurrence, regional recurrence, metastasis, breast cancer-specific survival, and overall survival. The authors[23] found differences ($p = 0.003$) in tumor size in groups with and without brain metastasis: 86.3% of patients with brain metastasis and 60.8% of patients without brain metastasis had a tumor ≤ 2 cm.

In the current study, we found a median overall survival of 52 months for patients with brain metastasis and primary tumor showing positivity for estrogen and progesterone receptors, of 44 months for patients with brain metastasis and primary tumor positive for c-erbB-2, and of 36.5 months for patients with brain metastasis and triple-negative carcinoma. Conceptually, CNS parenchymal metastases are of hematogenous origin.[14,16,18,24–27] Secondary CNS involvement usually occurs in advanced stages of the disease, and multiple metastases are observed in more than 50% of the cases. In most patients, metastasis to the lungs, liver, or bone precedes metastasis to the CNS.[6,14,20,24–26,28,29] In the current study, the presence of nodal metastasis was more common in patients without brain involvement (62.7%) than in patients with brain metastasis (36.4%; $p = 0.04$). This finding might be related to the hematogenous origin of metastases. Brain metastasis was observed in up to 30% of women with IBC who progressed to death. Similar rates of brain metastasis have been reported[2,4,5,9,15,25] in women

who underwent chemotherapy with epirubicin, docetaxel, and paclitaxel for visceral metastasis.

The development of brain metastasis in IBC is triggered by tumor clones, with PI3K mutations found in 40% to 70% of patients. Therefore, inhibition of the PI3K/AKT/mTOR pathway is a promising therapeutic strategy. However, most of the current agents targeting tumor lesions fail to penetrate the blood–brain barrier.[1,12,20,24,28]

Conclusion

Anatomopathological variables such as tumor size, c-erbB-2 expression, and triple-negative subtype can predict the presence of brain metastasis in patients with IBC. New mutations and/or genetic alterations have been studied to predict prognosis and improve the efficiency of the therapy for cases brain metastasis, including drugs that can successfully overcome the blood–brain barrier.

Authors' Contributions

EC: work design, scientific review, and writing of the manuscript MSM: work design and scientific review; and NBZ, JNAMS, and GBCN: data collection.

Ethics Declaration Statement

Approval was obtained from the Ethics Committee of Hospital Nossa Senhora da Conceição, Porto Alegre, RS, Brazil. The procedures used in the present study adhere to the tenets of the Declaration of Helsinki.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Eberst L, Bailleux C, Bachelot T. Prevention of brain metastases in human epidermal growth factor receptor 2-positive breast cancer. Curr Opin Oncol 2020;32(06):555–560

2 Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer 2006;107(04):696–704

3 Allison M. Martin, BS Daniel N. Cagney, MD Paul J. Catalano, Sc et al. Brain Metastasis in Newly diagnosed breast cancer: a Population-based Study. JAMA Oncol. 2017;3(08):1069–1077. doi:10.1001/jamaoncol.2017.0001

4 Komorowski AS, Warner E, MacKay HJ, Sahgal A, Pritchard KI, Jerzak KJ. Incidence of brain metastases in nonmetastatic and metastatic breast cancer: is there a role for screening? Clin Breast Cancer 2020;20(01):e54–e64

5 Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011;17(14):4834–4843

6 Graesslin O, Abdulkarim BS, Coutant C, et al. Nomogram to predict subsequent brain metastasis in patients with metastatic breast cancer. J Clin Oncol 2010;28(12):2032–2037

7 Minisini AM, Moroso S, Gerratana L, et al. Risk factors and survival outcomes in patients with brain metastases from breast cancer. Clin Exp Metastasis 2013;30(08):951–956

8 Niwińska A, Tacikowska M, Pieńkowski T. Occult brain metastases in HER2-positive breast cancer patients: frequency and response to radiotherapy. Acta Oncol 2007;46(07):1027–1029

9 Montagna E, Cancello G, D'Agostino D, et al. Central nervous system metastases in a cohort of metastatic breast cancer patients treated with trastuzumab. Cancer Chemother Pharmacol 2009;63(02):275–280

10 Pellerino A, Internò V, Mo F, Franchino F, Soffietti R, Rudà R Management of brain and leptomeningeal metastases from breast cancer. Int J Mol Sci 2020;21(22):8534

11 Babak MV, Zalutsky MR, Balyasnikova IV. Heterogeneity and vascular permeability of breast cancer brain metastases. Cancer Lett 2020;489:174–181

12 Ippen FM, Grosch JK, Subramanian M, et al. Targeting the PI3-K/Akt/mTOR pathway with the pan-Akt inhibitor GDC-0068 in PIK3CA-mutant breast cancer brain metastases. Neuro-oncol 2019;21(11):1401–1411

13 Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro-oncol 2021;23(06):894–904

14 Pedrosa RMSM, Mustafa DA, Soffietti R, Kros JM. Breast cancer brain metastasis: molecular mechanisms and directions for treatment. Neuro-oncol 2018;20(11):1439–1449

15 Yan M, Lü HM, Liu ZZ, et al. High risk factors of brain metastases in 295 patients with advanced breast cancer. Chin Med J (Engl) 2013;126(07):1269–1275

16 Atahan IL, Ozyigit G, Yildiz F, et al. Percent positive axillary involvement predicts for the development of brain metastasis in high-risk patients with nonmetastatic breast cancer receiving postmastectomy radiotherapy. Breast J 2008;14(03):245–249

17 Altundag K, Bondy ML, Mirza NQ, et al. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis. Cancer 2007;110(12):2640–2647

18 Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004;22(17):3608–3617

19 Evans AJ, James JJ, Cornford EJ, et al. Brain metastases from breast cancer: identification of a high-risk group. Clin Oncol (R Coll Radiol) 2004;16(05):345–349

20 Liu Y, He M, Zuo WJ, Hao S, Wang ZH, Shao ZM. Tumor size still impacts prognosis in breast cancer with extensive nodal involvement. Front Oncol 2021;11:585613

21 Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive biomarkers in breast cancer: Past, present and future. Semin Cancer Biol 2018;52(Pt 1):56–73

22 Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989;63(01):181–187

23 Fung F, Cornacchi SD, Vanniyasingam T, et al. Predictors of 5-year local, regional, and distant recurrent events in a population-based cohort of breast cancer patients. Am J Surg 2017;213(02):418–425

24 Watanabe J, Mitsuya K, Nakamoto S, et al. Leptomeningeal Metastasis in ER + HER2- Advanced Breast Cancer Patients: A Review of the Cases in a Single Institute Over a 15-year Period. Breast Cancer Res Treat 2021;189(01):225–236

25 Galanti D, Inno A, La Vecchia M, et al. Current treatment options for HER2-positive breast cancer patients with brain metastases. Crit Rev Oncol Hematol 2021;161:103329

26 Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. Med Oncol 2000;17(04):279–286

27 Kaplan A, Li MJ, Malani R. Treatments on the Horizon: Breast Cancer Patients with Central Nervous System Metastases. Curr Oncol Rep 2022;24(03):343–350. Doi: 10.1007/s11912-022-01206-2

28 Ben-Zion Berliner M, Yerushalmi R, Lavie I, et al. Central nervous system metastases in breast cancer: the impact of age on patterns of development and outcome. Breast Cancer Res Treat 2021;185(02):423–432

29 Koniali L, Hadjisavvas A, Constantinidou A, et al. Risk factors for breast cancer brain metastases: a systematic review. Oncotarget 2020;11(06):650–669

Appendix: Clinico-pathologic data from patients with invasive breast cancer and central nervous system metastasis

Case	Age	Tumor size/stage	Nodal status	ER	PR	HER-2	Ki-67	Metastasis topography	Metastasis size	Number of metastases
1	40	2.5 cm/T2	N2a	−	−	+	40%	Right frontal lobe	3.3 × 3.2 cm	1
2	55	2.0 cm/T1	N0	+	−	+	20%	Right cerebellar hemisphere	5.1 × 2.8 cm	1
3	70	2.5 cm/T2	N0	+	+	−	50%	Left cerebellar hemisphere	4.8 × 2.6 cm	1
4	53	6.0 cm/T3	N0	−	−	+	20%	Temporal lobe	2.5 × 2.3 cm	1
5	30	2.0 cm/T1	N1a	+	+	+	40%	Left occipital lobe	5.2 × 4.0 cm	1
6	45	3.5 cm/T2	N0	+	+	+	40%	Left cerebellar hemisphere	3.2 × 2.3 cm	1
7	59	2.5 cm/T2	N0	+	+	−	30%	Left frontotemporal region	4.5 × 3.7 cm	1
8	62	6.0 cm/T3	N2b	+	+	+	20%	Left frontal lobe	3.9 × 3.2 cm	1
9	31	2.0 cm/T1	N0	−	−	+	30%	Right frontal lobe	4.4 × 2.5 cm	1
10	53	3.0 cm/T2	N0	−	−	+	40%	Left frontal lobe	3.0 × 2.5 cm	1
11	73	4.0 cm/T2	N0	+	−	−	30%	Left cerebellar hemisphere	3.0 × 2.0 cm	1
12	68	3.0cm/T2	N0	−	−	+	70%	Right cerebellar hemisphere and left frontal lobe	2.2 × 1.5 cm and 1.9 × .8 cm	2
13	38	4.0 cm/T2	N1c	+	+	+	80%	Left cerebellar hemisphere	3.8 × 2.7 cm	1
14	60	2.5 cm/T2	N1a	−	−	+	30%	Right cerebellar hemisphere	4.2 × 3.0 cm	1
15	64	6.0 cm/T3	N2a	+	+	−	10%	Occipital lobe and left cerebellar hemisphere	5.4 × 3.4 cm, 2.7 × 2.0 cm, and 0.4 × 0.4 cm	3
16	50	4.0 cm/T2	N0	−	−	−	20%	Left cerebellar hemisphere	2.4 × 2.0 cm	1
17	38	7.5 cm/T3	N0	−	−	+	40%	Left and right cerebellar hemispheres	2.2 × 1.6 cm and 0.6 × 0.5 cm	2
18	43	3.5 cm/T2	N0	+	+	−	10%	Left cerebellar hemisphere, right cerebellar hemisphere, and left frontal lobe	5.5 × 4.8 cm, 3.2 × 1.8 cm, and 1.8 × 1.0 cm	3
19	33	4.5 cm/T2	N0	−	−	−	40%	Right cerebellar hemisphere, left cerebellar hemisphere, and occipital lobe	3.4 × 3.3 cm, 2.0 × 1.2 cm, and 0.7 × 0.7 cm	3
20	31	4.0 cm/T2	N0	−	−	−	60%	Left frontal lobe	2.0 × 1.3 cm	1
21	58	2.0 cm/T1	N1a	−	−	−	70%	Right posterior fossa	4.0 × 2.5 cm	1
22	31	2.0 cm/T1	N0	−	−	+	30%	Right frontal lobe	4.4 × 2.5 cm	1

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor-2; PR, progesterone receptor.

291 Internal Carotid Artery Aneurysms Treated with Fred, Silk, and Pipeline Stents: A Cross-Sectional Study

291 Aneurismas na Artéria Carótida Interna Tratados com os Stents Fred, Silk e Pipeline: Um Estudo Transversal

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Abstract

Objective Intracranial aneurysms (IAs) are present in ~ 2 to 5% of the population. Several treatments have been used, including endovascular options such as flow diverter devices (FDDs). The present study retrospectively analyzed the effectiveness of three FDDs in the treatment of 291 aneurysms in the internal carotid artery. The devices analyzed were the flow-redirection endoluminal device (FRED), the SILK Embolization Device and the PIPELINE Embolization Device (PED).

Method This is a cross-sectional study which evaluates the outcome of control arteriography. The O'Kelly-Marotta (OKM) Scale was used to assess the degree of filling and flow stasis in the aneurysm 12 months after surgery.

Results Conjoining the result of the three devices, most aneurysms (87.9%) were from the classification C-D, that is, they presented complete or almost complete aneurysmal occlusion. However, 6.6% did not obtain aneurysm occlusion, so they were classified as belonging to group A. In group B, a subocclusion was presented in 5.5%. In addition, by analyzing individually the result of each device, there was a bigger proportion of those classified in the group A among those who used SILK and in the group C-D among those who used FRED. Regarding complications, 10 cases were found, corresponding to 4.23% of all 236 patients. Therefore, four of these patients had complications when treated with PED; this proportion is higher than expected concerning the other groups.

Conclusion The three devices are safe choices. Particularly, the FRED was found to be the most effective in treating internal carotid artery aneurysms.

Keywords
- aneurysm
- intracranial
- endovascular
- stents

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Resumo

Objetivo Aneurismas intracranianos (AIs) estão presentes em ~ 2 a 5% da população. Vários tratamentos têm sido utilizados, incluindo opções endovasculares, como redirecionadores de fluxo (RFs). O presente estudo analisou retrospectivamente a eficácia de três dispositivos: dispositivo endoluminal de redirecionamento de fluxo (FRED, na sigla em inglês), dispositivo de embolização SILK e dispositivo de embolização pipeline (PED, na sigla em inglês), no tratamento de 291 aneurismas da artéria carótida interna.

Método Trata-se de um estudo transversal, avaliando o desfecho quanto ao grau de enchimento e a estase de fluxo no aneurisma com arteriografia de controle após 12 meses da cirurgia usando a Escala O'Kelly-Marotta (OKM).

Resultados Combinando o resultado dos três dispositivos, mais aneurismas (87,9%) eram do grupo D ou C, ou seja, apresentaram oclusão aneurismática completa ou quase completa; 5,5% apresentaram suboclusão, classificação B, e 6,6% não obtiveram oclusão do aneurisma, sendo da classificação A. Além disso, ao analisar individualmente o resultado de cada aparelho, houve maior proporção daqueles classificados no grupo A entre os que usaram SILK, e C-D entre os que usaram o FRED. Quanto às complicações, foram encontrados 10 casos, ou seja, 4,23% de todos os 236 pacientes, 4 destes pacientes tiveram complicações quando tratados com PED, sendo essa proporção maior do que o esperado em relação aos demais grupos.

Conclusão Os três dispositivos são escolhas seguras, sendo o FRED o mais eficaz no tratamento de aneurismas de artéria carótida interna.

Palavras-chave

- aneurisma
- intracraniano
- endovascular
- stent

Introduction

Intracranial Aneurysms (IAs) are present in ~ 2 to 5% of the population and they are the most common cause of nontraumatic spontaneous subarachnoid hemorrhage.[1] Moreover, unruptured IA presents a risk of cerebrovascular accident (CVA), coma or death.[2] There is no universal treatment for aneurysms, so therapy must be individualized for each patient.[3] Several treatments have been used over the years, from medical management under supervision to open surgical interventions and, more recently, endovascular options.[2–4] The different endovascular techniques include: coils system, stent-assisted coiling, balloons, and flow diverter devices (FDDs).[5]

The medical evidence for FDDs for intracranial aneurysms is based on numerous prospective and retrospective studies that assess their safety and efficacy.[6–8] There are currently several FDDs available, such as the Pipeline Embolization Device (PED; Covidien, Irvine, California, USA), the flow redirection endoluminal device (FRED; MicroVention, Tustin, California, USA), and the SILK Flow Diverter (SILK; Balt Extrusion, USA).[9–11]

Flow diverter devices have high metallic coverage and low porosity; subsequently, they can influence the hemodynamics of the aneurysm through the remodeling of the main artery vessels, thus inducing aneurysmal thrombosis and, subsequently, promoting repair of the tunica intima of the aneurysm neck[12,13] by overcoming the limitations of conventional stents.[14,15]

In the last decade, flow diverter therapy has caused a revolution in the treatment of unruptured aneurysms on a never-before-seen scale.[11] Therefore, it is essential to continue comparative analyzes concerning the effectiveness of the devices used in this endovascular treatment. Thus, the present study analyzed the safety and efficacy of three FDDs: FRED, SILK and PED, in the treatment of 236 patients with 291 aneurysms in the internal carotid artery.

Method

This is a cross-sectional study, whose data were obtained through the analysis of clinical and radiological information. These data were found in the medical records of patients being treated for internal carotid aneurysms with an endovascular procedure using FRED, PED or SILK stents in the last 4 years.

Ethical Aspects

All patients in the present article were studied according to the precepts of the Declaration of Helsinki and the Nuremberg Code, respecting the Standards for Research Involving Human Subjects of the National Health Council and the medical records only began to be analyzed after the institution's approval.

Patient and Device Selection

It was standardized that adult patients ($\geq$ 18 years old) with unruptured aneurysms in segments C1 to C7 of the internal carotid artery,[16] which followed the same protocols with antiplatelet agents and postoperative follow-up. All patients were treated with FRED, SILK or PED stents. The choice of device used was defined according to the availability of the device in the neurosurgery service, each one being used in a series of consecutive cases. Pipeline embolization devices

were initially used, followed by SILK, and finally, when double-layer stents became available, FRED was used. We did not consider the dimensions of the aneurysm or demographic variables such as gender, age, or ethnicity. Thus, we focused on simulating the challenges encountered in the care of this pathology based on available resources and patient variability.

Antiplatelet Therapy

Was used Prasugrel 10 mg started 10 days before the surgical procedure, being later maintained for 6 months postprocedure, and acetylsalicylic acid 100 mg was kept in continuous use.

Devices

The PED is a self-expanding, cylindric, braided device consisting of 48 strands of cobalt-chromium and platinum-tungsten wire.[17] The SILK is a flexible, self-expanding device specifically designed to produce a hemodynamic flow diversion and reconstruct laminar flow in the parent artery.[18,19] The FRED device consists of a braided self-expandable closed-cell dual-layer stent (also referred to as a "stent within a stent").[10]

For choosing the ideal size of the device used, all patients underwent angiography with three-dimensional reconstruction, and the anatomy and the measure of the proximal and distal diameter of the aneurysm in the main artery which the device should be was delimited.

Follow-Up

The 12-month post-treatment evaluation was performed using the O'Kelly-Marotta (OKM)[20] Scale. Each aneurysm is classified with a letter which represents the degree of filling (A, total filling; B, subtotal filling; C, entry remaining; D, no filling). The primary endpoint for treatment efficacy was complete or near-complete occlusion of the aneurysm (OKM C or D).

Statistical Analysis

The data were organized in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). The tables were built using the tools available in Microsoft Word (Microsoft Corporation, Redmond, WA, USA), Excel and Bioestat 5.5 software. All tests were performed using Bioestat 5.5 software. Quantitative variables were described as minimum, maximum, mean $\pm$ standard deviation (SD) and qualitative variables as frequency and percentage. The independence or association between two categorical variables was tested using the chi-squared test or the Fisher exact test, depending on the case. Likewise, the significant associations were detailed using standardized residual analysis to identify the categories that contributed the most to the result. Results with $p \leq 0.05$ (bilateral) were considered statistically significant.

Results

Epidemiology

A total of 236 patients were included in the study. Most were female (90.3%). In addition, 41.1% of the individuals were aged between 40 and 59 years old, and 35.2% of the individuals were elderly (60 to 80 years old) (►**Table 1**). The mean age was 53.5 $\pm$ 12.6 years old, ranging from 18 to 80 years old.

Table 1 Epidemiological characteristics of the patients

Variable	Frequency	Percentage
Gender		
Female	213	90.3
Male	21	8.9
Uninformed	2	0.8
Age (years old)		
18–19	1	0.4
20–39	32	13.6
40–59	97	41.1
60–80	83	35.2
Uninformed	23	9.7

Source: Patient records
The percentages are relative to the total number of participants ($n = 236$).

As for the number of aneurysms, 291 were detected. It is worth noting that the total number of aneurysms is greater than the number of participants, as in 22% of the patients, there was an incidence of multiple aneurysms. A total of 223 (76.6%) aneurysms were located in C6; 44 (15.1%) in C7; 13 (4.5%) in C4; 9 (3.1%) in C5; and 1 in C3 and C2.

Regarding the size of the aneurysm, the vast majority of 256 (88%) were small, while 19 (6.5%) were medium in size (►**Table 2**). To access the ability to generalize the results, 95% confidence intervals (CIs) were calculated for the proportion. The narrower the range, the more certain the proportion in the population that is represented by this sample. Furthermore, if two CIs do not overlap, the two proportions will likely be different in the population. This is the case between small and medium aneurysms. Notably, the occurrence of small aneurysms is significantly higher than that of medium aneurysms, indicating that small-sized aneurysms, which are < 7 millimeters, have a larger population proportion than medium-sized, large, and giant aneurysms.

Table 2 Size of aneurysms

Variable	Frequency	Percentage	95%CI
Size			
Small (< 7 mm)	256	88.0	83.5–91.4
Medium (7–9,9mm)	19	6.5	4.1–10,2
Large (10–19,9mm)	13	4.5	2.5–7,7
Giant ($\geq$ 20mm)	3	1.0	0.3–3,2

Abbreviations: CI, confidence interval; mm, millimeter.
Source: Patient records.
The percentages are relative to the total number of aneurysms ($n = 291$).
95%CI for the proportion

Table 3 Evaluation of the three devices together using the O'Kelly-Marotta scale

Variable	Frequency	Percentage	95%CI
(OKM)			
A	19	6.6	4.1–10.2
B	16	5.5	3.3–8.9
C-D	256	87.9	82.8–90.8

Abbreviation: CI, confidence interval.
Source: Patient records,
Note: (A, total filling; B, subtotal filling; C, remaining entry; D, without filling)
The percentages are relative to the total number of aneurysms ($n = 291$)
95%CI for the proportion

Table 4 Comparison of each device using the O'Kelly-Marotta scale

Variable	FRED ($n = 196$)	PIPELINE ($n = 40$)	SILK ($n = 53$)	*p-value*
(OKM)				0.010
A	*7 (3.6)**	4 (9.52)	*8 (15.1)*†	
B	8 (4.1)	4 (9.52)	4 (7.5)	
C-D	*181 (92.3)*†	34 (80.9)	*41 (77.4)**	

Source: Patient records,
Note: (A, total filling; B, subtotal filling; C, remaining entry; D, without filling)
Categorical variables are displayed as *n* (%). Percentages are relative to the total for each column. The chi-squared test was used with $p < 0.05$ (p-value = 0.010).
*this frequency was lower than would be expected by chance.
†this frequency was higher than would be expected by chance.

Efficacy

There were 291 aneurysms in our study; 195 were treated with the FRED device, 53 with the SILK device, and 42 with the PED device.

Regarding the effectiveness of endovascular treatment, initially, the combined results of the 3 devices revealed that the majority of aneurysms (87.9%) were from the C-D group (95%CI = 83.6–92.2). As a result, those with complete or near-complete aneurysmal occlusion. 5.5% (95%CI = 3.3 - 8.9) had a sub-occlusion, which was categorized as the B group, and 6.6% had no aneurysm occlusion (95%CI = 3.4% - 10.2%) classification A. (►**Table 3**).

Analyzing the results of each FDD individually (►**Table 4**), it was observed that the device and degree of filling were significantly associated ($p = 0.010$) by the 53 aneurysms treated with the SILK device, of which 8 (15.1%) had filling degree A. This proportion was bigger (†) than expected. Of the aneurysms treated with FRED, 181 (92.3%) had a degree of filling C-D; this proportion was also bigger than expected. In other words, there was a greater proportion of those classified in group A among those who used SILK, and C-D among those who used FRED compared with aneurysms in which they used the other devices. Likewise, 3.6% of the patients in whom FRED was applied obtained classification A. Besides this proportion being lower (*) than would be expected by random.

►**Table 5** elucidates the association between the device and the presence of complications per patient. Among all procedures, there is a 4.23% rate of complications and there was a significant association between the 2 variables ($p = 0.029$). In addition to the patients treated with the PIPELINE device, 4 (12.5%%) had complications, being two CVA, one hemorrhagic and one ischemic due to occlusion of the stent, a femoral artery dissection and a carotid-cavernous fistula. In comparison with the other groups, this proportion is higher than expected. Additionally, 28 patients (87.5%) had no complications. This is a lower frequency than would otherwise be predicted by chance. Regarding the SILK device, there was one thrombosis with hemiparesis and among the five complications associated with FRED treatment, four were CVAs, three hemorrhagic and one ischemic, and there was one case of postsurgical hemianopia.

It was also evaluated whether there was a correlation between the presence of complications and the size of the aneurysm in the treated patient. For example, in the group with complications, 80% of patients had a small aneurysm size and 20% had no small size, while in the uncomplicated group, 89.4% of patients had a small aneurysm size. However, this difference was not statistically significant ($p = 0.303$). Similarly, there was no significant association in medium ($p = 0.555$), large ($p = 1{,}000$), or giant ($p = 0.122$) size.

Table 5 Comparison of the presence of complications between the different devices used in patients with aneurysms of the internal carotid artery

Variable	FRED ($n = 161$)	PIPELINE ($n = 30$)	SILK ($n = 45$)	*p-value*
Complicações				0.029
Without complications	154 (96.9)	*28 (87.5)**	44 (97.8)	
With complications	5 (3.1)	*4 (12.5)*†	1 (2.2)	

Source: Patient records
Categorical variables are displayed as *n* (%). Percentages are relative to the total for each column.
The chi-squared test was used with $p < 0.05$ (p-value = 0.029).
*: this frequency was lower than would be expected by chance.
†: this frequency was higher than would be expected by chance.

Discussion

It was observed that the female gender predominated, totaling 213 patients out of a total of 236 (90.3%), with a mean age of 53.5 years old, ranging from 12.6 years to more or less, ranging from patients with 18 to 80 years old. According to the literature, regarding gender, the systematic review by Vlak et al.[21] analyzed the epidemiology in 29 studies that discussed the prevalence in men and women separately of unruptured intracranial aneurysms, identifying a higher prevalence in women than in men. Regarding age, the study by Kraemer et al.[3] noted that most diagnosed patients are in the 6th or 7th decade of life and that in the modern imaging age, many with asymptomatic carotid aneurysms are discovered accidentally. In addition, Binh et al.[22] found a mean age of 50 years old, with a range from 22 to 76 years old, similar to the present study.

Based on the results, the size of the vast majority of aneurysms found was small ($<$ 7 mm), which corresponds to 88% of the total, $\sim$ 256 aneurysms; 19 medium-sized aneurysms (7 to 9.9 mm), corresponding to 6.5% of the total; 13 large-sized aneurysms (10 to 19.9 mm), corresponding to 4.5% and 3 giant-sized aneurysms ($\geq$ 20 mm), corresponding to 1% of the total of 291 aneurysms. The vast majority of small-sized aneurysms are widely reported in the literature. The literature review analyzed 182 articles, which despite diverging in the definition of size, pointed out that small aneurysms are the most mentioned in the literature, which is probably due to the extensive research carried out on small IAs and the implication of their size in the risk of rupture.[23–25] These data support the results found in the present study.

Our study evaluated 53 aneurysms that used the SILK device. A total of 35 (77.4%) of these aneurysms had a satisfactory degree of complete or near-complete occlusion, 4 aneurysms had sub-occlusion, and 8 had no occlusion, the latter being a frequency above what would be expected by chance. The DIVERSION[26] study, a French cohort with 118 aneurysms, 71 of which were located in the internal carotid artery, treated with SILK, showed a satisfactory occlusion rate in 82.2% of cases in the 12-month follow-up. In addition to this article, Pumar et al.[27] retrospectively observed complete occlusion in 78.1% of aneurysms in 128 aneurysms after 12 months, corroborating these findings, and in meta-analyses, complete aneurysm occlusion rates with SILK ranged from 76 to 89.6% in between 6 to 12 months.[12,28]

In the present study, 42 aneurysms were treated with the PIPELINE device, with 34 (80.9%) achieving satisfactory aneurysm occlusion, 4 (9,52%) had sub-occlusion, and in 4 aneurysms there was no occlusion. These data are similar to those found in two large prospective, single-arm, multicenter studies. The PREMIER,[29] which also assessed the PIPELINE in the treatment of unruptured internal carotid artery aneurysms in 141 patients, achieved total aneurysm occlusion in 81.9%, and the SHIELD[30] study, which observed the use of PIPELINE in 205 aneurysms, with 77.2% of total aneurysmal occlusion after 12-months of follow-up.

Regarding the FRED Stent, of the 196 aneurysms that were treated with this device, 181 (92.3%) achieved satisfactory aneurysmal occlusion after a 12-month follow-up angiography, whose frequency was higher than that expected by chance. Similar results were found in a large European multicenter study[8] with 531 patients and 579 aneurysms. In that series, the overall rate of complete aneurysm occlusion was 69.2% at 6 months and 91.3% at 12 months of follow-up. In addition, the SAFE,[31] prospective, multicenter, single-arm study evaluated FRED in 103 aneurysms with complete aneurysmal occlusion in 73,3% of cases after assessment by 12-month angiography. We believe that the better results related to the FRED are due to its more recent double-layer technology, which allows the device to act as a stent within another stent. As a result of its increased ability to remodel, the affected vessel may also be repositioned with up to 50% release.

In the present study, there were no deaths, and in a total of 10 cases, we found complications, accounting for 4.23% of all patients treated with the 3 devices. Among the complications observed are six CVAs, one femoral artery dissection, one carotid-cavernous fistula, one thrombosis with hemiparesis and one postsurgical hemianopia. There were no deaths in the present study. The literature indicates that permanent morbidity related to the procedure was reported in all 18 studies in the review by Briganti et al.,[28] with an average rate of 3.5%, with CVA being the most common complication, ranging from 1 to 14.2% among all complications.[28] In addition, mortality ranging from 0.5 to 8% (mean rate of 3.5%) was observed in the present study. Another literature review with meta-analysis[32] pointed out that during clinical follow-up (mean, 8.5 months), the postoperative mortality rate was 1.3% and the late neurological complication rate was 2.6%. We understand that the higher results related to complications in our study in relation to the literature may be due to the higher rate than expected by chance of the PED device, and this can be justified by the fact that this is the first device used in the case series, being less updated than the other devices and that complications occurred in the first patients submitted by this team to endovascular interventions.

There were limitations in our study: firstly, different forms of scales used to describe treatment efficacy are observed in the literature. For example, we used the O'Kelly Marota[22] scale to determine the degree of filling of the aneurysm, adopting the classification C and D as satisfactory. However, the PREMIER[29] study uses the Raymond-Roy[33] scale, in which class 1 is defined as a complete obliteration of the aneurysm, as well as in the DIVERSION[26] study, which concludes the analysis assuming satisfactory occlusion defined as 3 or 4 on the Kamran scale.[34] Therefore, we considered the comparison of these best outcomes according to the scale used by the methodology of each article discussed.

In addition, despite generalizing the discussion about FDDs, we did not analyze all those available on the market, such as Surpass Streamline (Stryker, UK) and Tubridge (MicroPort Medical Company, China), for reasons of availability of the device in the service. These devices may have

different results and perspectives regarding treatment. Moreover, this was a single-center retrospective study and cannot be generalizable to other centers.

Finally, with the advancement of endovascular procedures in neurosurgery, there is a need for constant updates. For this reason, the present study aims to help the studies of devices that are at the forefront of the treatment of intracranial aneurysms, as well as to seek to optimize positive outcomes and reduce possible deleterious effects of intracranial pathologies. Therefore, it is worth emphasizing that more studies in this area are important to further consolidate knowledge on this topic.

Conclusion

Endovascular treatment of aneurysms located in the internal carotid artery with the FRED, SILK, and PED devices is safe and effective, presenting high rates of satisfactory aneurysm occlusion (complete or near-complete occlusion), with low permanent neurological complications; in addition, our findings indicate that there is a statistically significant advantage in the use of FRED.

Institution where the study took place
Universidade do Estado do Pará, UEPA. This research has its own funding.

Ethics Committee Approval Number
5.218.761 (CAAE: 48444321.6.0000.5174)

Conflict of Interests
The authors have no conflict of interests to declare.

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References

1 Zhao J, Wang R, Zhang D, et al. A comparative study of 43 patients with mirror-like intracranial aneurysms: risk factors, treatment, and prognosis. Neuropsychiatr Dis Treat 2014;2231;. Doi: 10.2147/ndt
2 Silva NA, Shao B, Sylvester MJ, Eloy JA, Gandhi CD. Unruptured aneurysms in the elderly: perioperative outcomes and cost analysis of endovascular coiling and surgical clipping. Neurosurg Focus 2018;44(05):E4. Doi: 10.3171/2018.1.focus17714
3 Kraemer CJK, Zhou W. Carotid Aneurysm Review. Int J Angiol 2019;28(01):017–019. Doi: 10.1055/s-0039-1677675
4 Rajah G, Narayanan S, Rangel-Castilla L. Update on flow diverters for the endovascular management of cerebral aneurysms. Neurosurg Focus 2017;42(06):E2. Doi: 10.3171/2017.3.focus16427
5 Alderazi YJ, Shastri D, Kass-Hout T, Prestigiacomo CJ, Gandhi CD. Flow diverters for intracranial aneurysms. Stroke Res Treat 2014; 2014:415653. Doi: 10.1155/2014/415653
6 Kallmes DF, Brinjikji W, Cekirge S, et al. Safety and efficacy of the Pipeline embolization device for treatment of intracranial aneurysms: a pooled analysis of 3 large studies. J Neurosurg 2017;127 (04):775–780. Doi: 10.3171/2016.8.jns16467
7 Becske T, Kallmes DF, Saatci I, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology 2013;267(03):858–868. Doi: 10.1148/radiol.13120099
8 Killer-Oberpfalzer M, Kocer N, Griessenauer CJ, et al. European Multicenter Study for the Evaluation of a Dual-Layer Flow-Diverting Stent for Treatment of Wide-Neck Intracranial Aneurysms: The European Flow-Redirection Intraluminal Device Study. AJNR Am J Neuroradiol 2018;39(05):841–847. Doi: 10.3174/ajnr.a5592
9 Kocer N, Islak C, Kizilkilic O, Kocak B, Saglam M, Tureci E. Flow Redirection Endoluminal Device in treatment of cerebral aneurysms: initial experience with short-term follow-up results. J Neurosurg 2014;120(05):1158–1171. Doi: 10.3171/2014.1.jns131442
10 Möhlenbruch MA, Herweh C, Jestaedt L, et al. The FRED flow-diverter stent for intracranial aneurysms: clinical study to assess safety and efficacy. AJNR Am J Neuroradiol 2015;36(06):1155–1161. Doi: 10.3174/ajnr.a4251
11 Chancellor B, Raz E, Shapiro M, et al. Flow Diversion for Intracranial Aneurysm Treatment: Trials Involving Flow Diverters and Long-Term Outcomes. Neurosurgery 2020;86(Suppl 1):S36–S45. Doi: 10.1093/neuros/nyz345
12 Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke 2013;44(02):442–447. Doi: 10.1161/strokeaha.112.678151
13 Ye G, Zhang M, Deng L, Chen X, Wang Y. Meta-Analysis of the Efficiency and Prognosis of Intracranial Aneurysm Treated with Flow Diverter Devices. J Mol Neurosci 2016;59(01):158–167. Doi: 10.1007/s12031-016-0723-x
14 Zhou G, Su M, Zhu YQ, Li MH. Efficacy of Flow-Diverting Devices for Cerebral Aneurysms: A Systematic Review and Meta-analysis. World Neurosurg 2016;85:252–262. Doi: 10.1016/j.wneu.2015.09.088
15 Burrows AM, Cloft H, Kallmes DF, Lanzino G. Periprocedural and mid-term technical and clinical events after flow diversion for intracranial aneurysms. J Neurointerv Surg 2015;7(09):646–651. Doi: 10.1136/neurintsurg-2014-011184
16 Bouthillier A, van Loveren HR, Keller JT. Segments of the internal carotid artery: a new classification. Neurosurgery 1996;38(03): 425–432, discussion 432–433. Doi: 10.1227/00006123-199603000-00001
17 Shapiro M, Raz E, Becske T, Nelson PK. Variable porosity of the pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy. AJNR Am J Neuroradiol 2014;35(04):727–733. Doi: 10.3174/ajnr.a3742
18 Kulcsár Z, Ernemann U, Wetzel SG, et al. High-profile flow diverter (silk) implantation in the basilar artery: efficacy in the treatment of aneurysms and the role of the perforators. Stroke 2010;41(08): 1690–1696. Doi: 10.1161/strokeaha.110.580308
19 Berg P, Iosif C, Ponsonnard S, Yardin C, Janiga G, Mounayer C. Endothelialization of over- and undersized flow-diverter stents at covered vessel side branches: An in vivo and in silico study. J Biomech 2016;49(01):4–12. Doi: 10.1016/j.jbiomech.2015.10.047
20 O'kelly CJ, Krings T, Fiorella D, Marotta TR. A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents. Interv Neuroradiol 2010;16 (02):133–137. Doi: 10.1177/159101991001600204
21 Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 2011;10(07):626–636. Doi: 10.1016/s1474-4422(11)70109-0
22 Binh NT, Luu VD, Thong PM, et al. Flow diverter stent for treatment of cerebral aneurysms: A report of 130 patients with 134 aneurysms. Heliyon 2020;6(02):e03356. Doi: 10.1016/j.heliyon.2020.e03356
23 Merritt WC, Berns HF, Ducruet AF, Becker TA. Definitions of intracranial aneurysm size and morphology: A call for standardization. Surg Neurol Int 2021;12:506. Doi: 10.25259/sni_576_2021

24 Morita A, Kirino T, Hashi K, et al; UCAS Japan Investigators. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med 2012;366(26):2474–2482. Doi: 10.1056/NEJMoa1113260
25 International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms–risk of rupture and risks of surgical intervention. N Engl J Med 1998;339(24):1725–1733. Doi: 10.1056/nejm199812103392401
26 Gariel F, Marnat G, Barreau X, et al; DIVERSION investigators. Safety and efficacy of the Silk flow diverter: Insight from the DIVERSION prospective cohort study. J Neuroradiol 2021;48(04):293–298. Doi: 10.1016/j.neurad.2020.06.006
27 Pumar JM, Banguero A, Cuellar H, et al. Treatment of Intracranial Aneurysms With the SILK Embolization Device in a Multicenter Study. A Retrospective Data Analysis. Neurosurgery 2017;81(04):595–601. Doi: 10.1093/neuros/nyw123
28 Briganti F, Leone G, Marseglia M, et al. Endovascular treatment of cerebral aneurysms using flow-diverter devices: A systematic review. Neuroradiol J 2015;28(04):365–375. Doi: 10.1177/1971400915602803
29 Hanel RA, Kallmes DF, Lopes DK, et al. Prospective study on embolization of intracranial aneurysms with the pipeline device: the PREMIER study 1 year results. J Neurointerv Surg 2020;12(01):62–66. Doi: 10.1136/neurintsurg-2019-015091
30 Rice H, Martínez Galdámez M, Holtmannspötter M, et al. Periprocedural to 1-year safety and efficacy outcomes with the Pipeline Embolization Device with Shield technology for intracranial aneurysms: a prospective, post-market, multi-center study. J Neurointerv Surg 2020;12(11):1107–1112. Doi: 10.1136/neurintsurg-2020-015943
31 Pierot L, Spelle L, Berge J, et al. SAFE study (Safety and efficacy Analysis of FRED Embolic device in aneurysm treatment): 1-year clinical and anatomical results. J Neurointerv Surg 2019;11(02):184–189. Doi: 10.1136/neurintsurg-2018-014261
32 Arrese I, Sarabia R, Pintado R, Delgado-Rodriguez M. Flow-diverter devices for intracranial aneurysms: systematic review and meta-analysis. Neurosurgery 2013;73(02):193–199, discussion 199–200. Doi: 10.1227/01.neu.0000430297.17961.f1
33 Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. Stroke 2001;32(09):1998–2004. Doi: 10.1161/hs0901.095600
34 Kamran M, Yarnold J, Grunwald IQ, Byrne JV. Assessment of angiographic outcomes after flow diversion treatment of intracranial aneurysms: a new grading schema. Neuroradiology 2011;53(07):501–508. Doi: 10.1007/s00234-010-0767-5

The Role of Transforming Growth Factor Beta and Smad Receptors in Determining Prognosis in High-Grade Primary Brain Tumors: Glioblastoma Multiforme

O papel do fator de crescimento transformador beta e receptores smad na determinação do prognóstico em tumores cerebrais primários de alto grau: glioblastoma multiforme

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Abstract

Introduction High-grade primary brain tumors cause serious morbidity and mortality. This study aimed to investigate the role of transforming growth factor beta (TGF-β) and suppressor of mothers against decapentaplegic (Smad) receptors in high-grade primary brain tumors.

Material and Method Thirteen patients with a pathological diagnosis of glioblastoma multiforme were included in the study. Pathological preparations of each patient were analyzed retrospectively in histochemistry and immunohistochemistry laboratories. Transforming growth factor beta 1, TGF-β2, TGF-β3, Smad 1/2/3, Smad 6, and Smad 7 stainings were evaluated, and the immunoreactivity densities were examined.

Result We found out an increase in the expression of TGF-β1 and TGF-β3 protein. Regarding the inhibitin receptors, Smad 6 showed much more expression than Smad 7. Thus, we found that Smad 6 has a protective effect and role in the tissue. Immunhistochemically, TGF-β family stains, which are activated by types I-and -II

Keywords
- glioblastoma multiforme
- transforming growth factor beta
- smad proteins
- endothelial-mesenchymal transition

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receptors, and the stainless staining of the Smad family might also be showing that the TGF-β family is taking action with a secondary pathway other than the Smad family.
Conclusion In addition to Smad family receptors, Shc-GBR2, SARA, and Ras-Erk1/2 receptors should be investigated in future research. After that, the prognosis, diagnosis, and patient-based chemotherapy strategies for the treatment of glioblastoma multiforme may take a more prominent role.

Resumo

Objetivo Tumores cerebrais primários de alto grau causam morbidade e mortalidade graves. Este estudo teve como objetivo investigar o papel dos receptores fato de crescimento transformante beta (TGF-β) e mães contra homólogo decapentaplégico (Smad, na sigla em inglês) em tumores cerebrais primários de alto grau.
Métodos Treze pacientes com diagnóstico patológico de glioblastoma multiforme foram incluídos no estudo. As preparações patológicas de cada paciente foram analisadas retrospectivamente em laboratórios de histoquímica e imunohistoquímica. As colorações de TGF-β1, TGF-β2, TGF-β3, Smad 1/2/3, Smad 6, e Smad 7 foram avaliadas, e as densidades de imunorreatividade foram examinadas.
Resultados Encontramos aumento na expressão das proteínas TGF-β1 e TGF-β3. Em relação aos receptores de inibitina, o Smad 6 mostrou muito mais expressão do que o Smad 7. Assim, concluímos que o Smad 6 tem efeito e função protetores no tecido. As colorações imunohistoquímicas da família TGF-β, que são ativadas pelos receptores do tipo I e do tipo II, e as colorações menos da família Smad também podem estar mostrando que a família TGF-β está agindo com outra via secundária que não a família Smad.
Conclusão Assim como os estudos na família Smad, receptores como Shc-GBR2, SARA, Ras-Erk1/2 devem ser investigados em pesquisas futuras. Posteriormente, o prognóstico, o diagnóstico, e as estratégias de quimioterapia baseadas no paciente podem assumir um lugar mais priminente no futuro, no glioblastoma multiforme.

Palavras-chave
- glioblastoma multiforme
- fato de crescimento transformante beta
- proteínas smad
- transição endotelial-mesenquimal

Introduction

Primary high-grade tumors of the brain (glioblastoma multiforme, GBM) cause serious morbidity and mortality.[1,2] Previous studies have revealed that these cancers have drug resistance, such as BCNU (carmustine), due to differentiation in cell protein synthesis and DNA structures, and many agents, such as TGF-β, are effective at the molecular level.[3]

Epithelium-mesenchymal transition (EMT) is a morphogenic process in which epithelial cells lose their properties and acquire mesenchymal properties during the embryogenesis and progression of cancer. The EMT process is stimulated and regulated by many effectors. These effectors are growth factors (TGF-β, platelet-derived growth factor [PDGF], epidermal growth factor [EGF]), cytokines (IL-8), and extracellular matrix (ECM) components.[4,5]

In this study, the histological sections of the tumor, and the demographic data, treatment protocols, and prognoses of the patients who were operated on for an intracranial mass and had postoperative clinicopathological diagnosis of glioblastoma multiforme were retrospectively analyzed.

The TGF-β family and Smad receptors were revealed by histochemical and immunohistochemical staining from the removed tumor tissues. The clinical data were recorded with patients and/or their relatives, and their current clinical outcome, morbidity, and mortality were evaluated with the goal to examine the prognostic relationship of treatments with TGF-β and Smad receptors in tumor tissue.

Material and Method

This study was conducted with the approval of Manisa Celal Bayar University Faculty of Medicine, local ethics committee, decision number 20478486–198, dated 07.05.2014.

A total of 13 patients with a pathological diagnosis of glioblastoma multiforme operated on between November 2012 and April 2014 were included in the study. The pathological preparations of each patient were analyzed retrospectively in histochemistry and immunohistochemistry laboratories. The clinical information and treatment protocols of the patients were collected from the records of the relevant clinics, and the data about their current status and clinical course were collected by consulting the hospital records, patients, and/or patient relatives.

The samples were taken into 10% formalin solution for histological analysis. Samples taken for histological examination were routinely followed by paraffin after fixation in 10% formalin solution for 24 to 48 hours. After being left

under running water overnight, dehydration was performed in a graded series of 60%, 70%, 80%, 90% absolute alcohol. After the transparency process in xylene-alcohol and xylene, a paraffin embedding process was performed by passing through xylene-paraffin, paraffin 1, and paraffin 2. Five-µm-thick sections were taken from the blocks formed on lysine and grinded slides with a rotary microtome. The morphological evaluation was provided by routine hematoxylin-eosin staining on some of the sections.

The routine avidin-biotin indirect immunoperoxidase method was used as immunohistochemical analysis. The sections taken on lysine slides were kept at 60°C for 1 night for deparaffinization and then kept in xylene for 1 hour for chemical deparaffinization. For the rehydration process, 95%, 80%, 70%, 60% alcohol series were passed through decreasing alcohol series. Then, the samples were washed 3 times with phosphate buffer (phosphate buffer solution-PBS) for 5 minutes and incubated at room temperature with 3% H_2O_2 for 10 minutes; after that, they were washed three times with PBS for 5 minutes. For the permeabilization of the tissues, the sections kept in trypsin at 37°C for 15 minutes were washed 3 times for 5 minutes with PBS. After incubating with blocking solution for 1 hour, all primary antibodies (anti-TGF-β1, anti-TGF-β2, anti-TGF-β3, anti-Smad 1/2/3, anti-Smad 6, anti-Smad 7) were incubated at +4°C overnight. The next day, the samples were washed 3 times with PBS solution, then a biotinylated secondary antibody was added and incubated for 30 minutes. After the samples were washed 3 times for 5 minutes, streptavidin-peroxidase was added and kept at room temperature for 30 minutes. After staining with diaminobenzidine (DAB) for 2 to 5 minutes to determine the visibility of the immunohistochemical reaction, the samples were washed with distilled water. For the purpose of background staining, the samples were stained with Mayer's hematoxylin for 3 to 6 minutes, then the excess dye was washed with distilled water and covered with an immunohistochemical covering medium.

Transforming growth factor beta staining was done by antibodies numbered SC146, TGF-β2 staining SC90, TGF-β3 staining SC82, Smad ½/3 staining SC7960, Smad 6 staining SC13048, and Smad 7 staining SC11392 (Catalog No Ref 859043).

The immunoreactivity densities obtained as a result of staining were evaluated by the quantitative method and were considered as negative (-), weak (+), moderate (++), and severe (+++).

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 20.0 version software (IBM, New York, USA). Continuous variables were expressed as mean ± standard deviation. The chi-squared test or Fisher exact test (when the chi-squared test assumptions did not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups. A p-value < 0.05 was considered statistically significant.

Results

Eight patients were male, and 5 were female. The lowest age was 49 and the highest was 73, while the mean age was 60.3, and the median age was 60. Although K_i-67 mitosis indexes varied between 10 and 40%, the average K_i-67 index was 22.3%, and the median K_i-67 index was 20%. Survival of 5 to 11 months was observed in 6 patients. The clinical follow-up and survival of the patients are given in ►**Table 1**.

In the morphological evaluation performed after routine hematoxylin staining in the patient samples, giant cells were observed in the normal cortex structures in the tumor tissues. Cell cytoplasms could be easily distinguished by their eosinophilic staining and pycnotic nuclei. Necrotic areas were also selected in patches. In addition to tumor tissues, histological structures belonging to normal brain tissue cortex were observed in some patient samples (►**Fig. 1 a-h**).

As a result of the evaluation of factors that play a role in TGF-β and Smad pathway in patient samples, it was found that TGF-β1 and TGF-β3 immunoreactivities were strongly positive (+++), while TGF-β2 immunoreactivity was moderately positive (++) in tumor tissue (►**Fig. 2a-b**, **3a-b**, **4a-b**). While staining for all TGF-β1 and TGF-β2 was observed in the tumor cell cytoplasm, it was observed that TGF-β2 immunoreactivity was also positive in connective tissue.

Transforming growth factor beta immunoreactivity was calculated as 3 ± 0, while TGF-β2 immunoreactivity was 2.2 ± 0.42 and TGF-β3 immunoreactivity was calculated as 3.2 ± 0.42. When the values were compared statistically, it was found that there was a significant difference between the immunoreactivities of TGF-β1 and TGF-β3 and TGF-β2 ($p < 0.001$), while there was no statistically significant difference between the TGF-β1 and TGF-β3 immunoreactivities ($p > 0.05$) (►**Table 2**, **Graphic 1**).

While Smad 1/2/3 immunoreactivity of TGF-β family receptors was intermittently positive (+/−), Smad 6 immunoreactivity was considered weak (+) and Smad 7 immunoreactivity was considered negative in all patient samples (►**Fig. 5a-b**, **6a-b**, **7a-b**) When the immunoreactivities of Smad receptors were compared statistically, it was observed that there was only significance between Smad 6 and Smad 7 ($p < 0.001$), but not among the others (►**Table 2**, **Graphic 1**).

Discussion

Glioblastoma multiforme (GBM) is the most common and most malignant glial tumor among primary brain tumors. According to the data in the USA, gliomas constitute 60% of 17,000 primary brain tumors detected every year. It creates a heterogeneous group in terms of location, age, and gender. The management includes palliative treatment regimens including surgery, radiotherapy, chemotherapy, and radiosurgery. It may occur primarily or secondary after the progression of low-grade astrocytomas. Primary GBMs are more common (60%) over the age of 50, but secondary GBMs (40%) are more common in patients under the age of 45. In their pathophysiology, loss of heterozygosity (10q

Table 1 Demographic characteristics and immunohistochemical staining patterns of the patients

Smad 7	–	–	–	–	–	–	–	–	–	–	–	–	–
Smad 6	+	+	+	+	+	+	+	+	+	+	–	+	+
Smad 1/2/3	–	–	–	–	–	–	–	–	–	–	–	–	–
TGF β3	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
TGF β2	++	++	++	++	++	++	++	++	++	++	++	++	++
TGF β1	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Survival	Alive	Alive	Alive	Alive	Alive	6 months	Alive	5 months	8 months	Alive	10 months	11 months	6 months
KT	–	–	–	–	–	–	+	–	+	+	+	+	–
RT	+	+	+	+	+	+	+	+	+	+	+	+	+
K_i-67 (%)	30	25	15	30	15	40	20	30	15	10	25	15	20
Karnofsky Outcome Score	70	90	80	80	100	80	90	50	80	80	80	60	40
Karnofsky Income Score	50	80	40	60	90	70	70	40	50	70	70	50	20
Tumor Location	Frontal	Temporal	Temporal	Parietal	Temporal	Frontal	Frontal	Temporal	Parietal	Frontal	Parietal	Temporal	Frontal
Sex	M	M	F	M	M	F	M	F	M	M	M	F	F
Age	58	63	57	65	49	61	69	55	60	63	54	57	73
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13

Abbreviations: KT, chemotherapy; RT, radiotherapy.

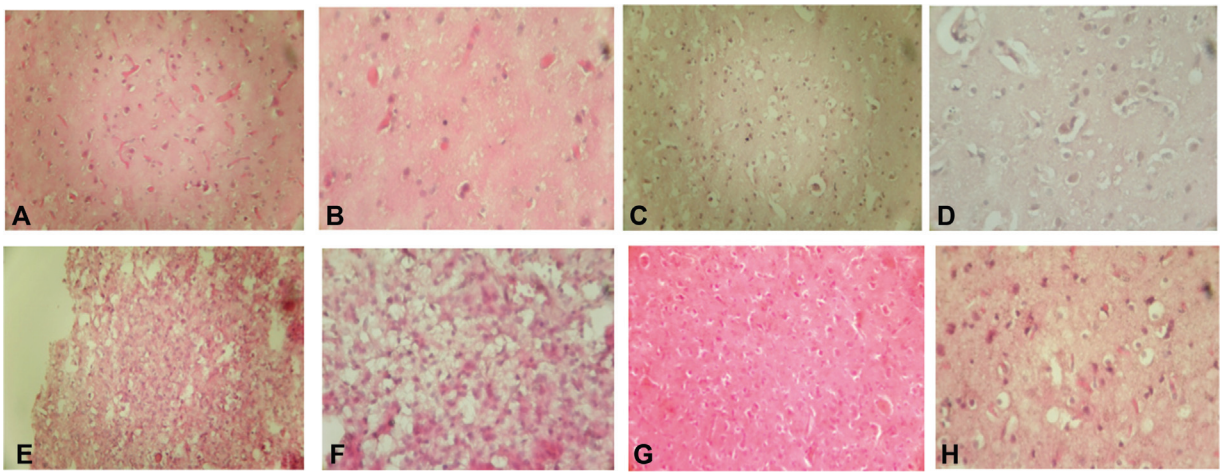


Fig. 1 (**A**) Normal brain tissue, parietal glial cells (hematoxylin & eosin × 200), (**B**) Normal brain tissue, parietal glial cells (hematoxylin & eosin × 400), (**C**) Parietally located high-grade glial tumor (GBM) (hematoxylin & eosin × 200), (**D**) Parietally located high-grade glial tumor (GBM) (hematoxylin & eosin x400), (**E**) Temporally located high-grade glial tumor (GBM) (hematoxylin & eosin × 200), (**F**) Temporally located high-grade glial tumor (GBM) (hematoxylin & eosin × 400), (**G**) Frontally located high-grade glial tumor (GBM) (hematoxylin & eosin × 400).

mutations); loss of p53, which is a tumor suppressor gene; epidermal growth factor receptor (EGFR) gene mutations; MDM2 overexpression, increased expression due to platelet derived growth factor α (PDGF-α); and 10q23.3 PTEN gene mutations. Although the temporal lobe is commonly involved (31%), it may arise from subcortical white matter almost anywhere in the brain. The brain stem, cerebellum, and spinal cord are less frequently involved. Its survival without treatment is 3 months, on average. The median survival reaches 12 months in patients who undergo surgery and, additionally, radiotherapy and chemotherapy. Less than 25% of patients can survive up to 2 years, and less than 10% of patients can survive up to 5 years. In the radiological evaluation, masses with irregular borders, nectoric areas in the central, and intensive digital edema, and peripheral contrast enhancement can be observed. –magnetic resonance spectroscopy shows an increase in the choline-creatine and lactate peaks, and a low N-acetylaspartate (NAA) peak[6].

The clinical applications of modern neurooncology depend on a consistent tumor classification. The absence of variation (variability, unusualness) provides a more accurate prediction of prognosis, and classification also forms the basis of the most important treatment advice that physicians offer to their patients. Neurooncologists use more or less the same treatment modalities for all patients with the same type of tumor. The importance of a coherent classification in neurooncology creates the need for great attention to this problem and encourages recurrent consideration of this indispensable topic.[7] Tumor classifications have been made many times since the beginning of the twentieth century, and with the help of developing technology, these classifications were either completely abandoned or revised in the light of new findings. Nowadays, it is not possible to talk about a classification with a definite reliability, which would provide the correct diagnosis and treatment selection depending on it.

As the name suggests, histological images of glioblastoma multiforme can vary. These tumors are poorly differentiated and may contain pleomorphic astrocyte cells with nuclear atypia, with increased mitotic activity. Glioblastomas show extensive cellular and molecular heterogeneity. Although the traditional view is that the tumor consists of a mass of malignant cells that grow uncontrollably, recent research shows that basic tumor cells create a microenvironment for the tumor by causing changes in normal tissues with the cytokines, chemokines, and growth factors they secrete. This microenvironment consists of many different cell groups in brain tumors. Among these, microglia, macrophage, astrocyte, oligondendrocyte, neurons, glial and neuronal progenitors, extracellular matrix, pericytes, and endothelial cells are the main ones. This neoplastic and non-neoplastic mixture determines the growth degree, invasiveness, immune response, and resistance to treatments of the tumor. Although there are many pathways associated with gliomas, TGF-β pathways play a very important role in establishing the above-mentioned features. There are several publications reporting the relationship between TGF-β levels and various advanced-stage tumors, high malignancy, and poor prognosis.[6,8]

Five isoforms of the TGFs family have been isolated so far. These are TGF-β1, TGF-β2, TGF-β3, TGF-β4, and TGF-β5. Of these, TGF-β1, TGF-β2, and TGF-β3 are expressed in mammalian tissue. The TGF-βs family participates in many functions, such as cell proliferation, differentiation, formation of extracellular matrix components, chemotaxis, immunosuppression, and cell death regulation. Transforming growth factors beta are secreted by the mesenchyme, connective tissue, endothelium, platelets, bone, and immune system cells.

Transforming growth factor beta shows its effects in the cell through many molecules (MAPKs, JNK, p38, p13K Kinases, PP'A phosphatases, Rho and Smad families). However,

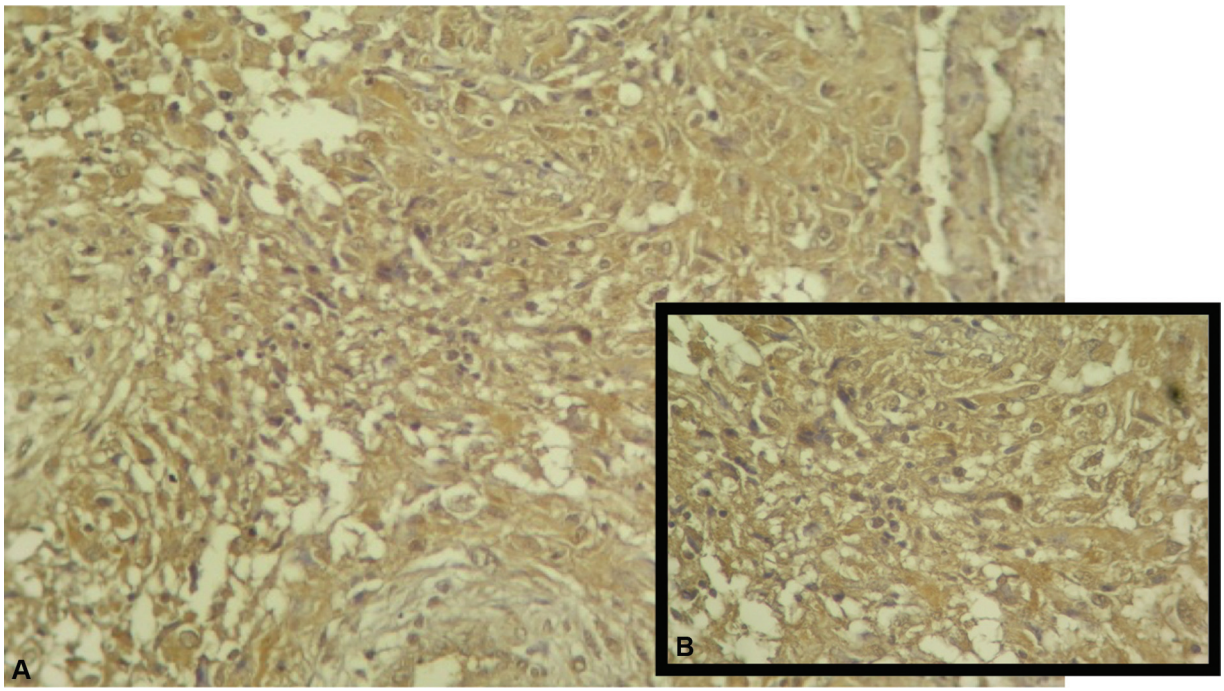


Fig. 2 Transforming growth factor beta 1 immunoreactivity in tumor (GBM) tissue. (**A**) x200, (**B**) x400.

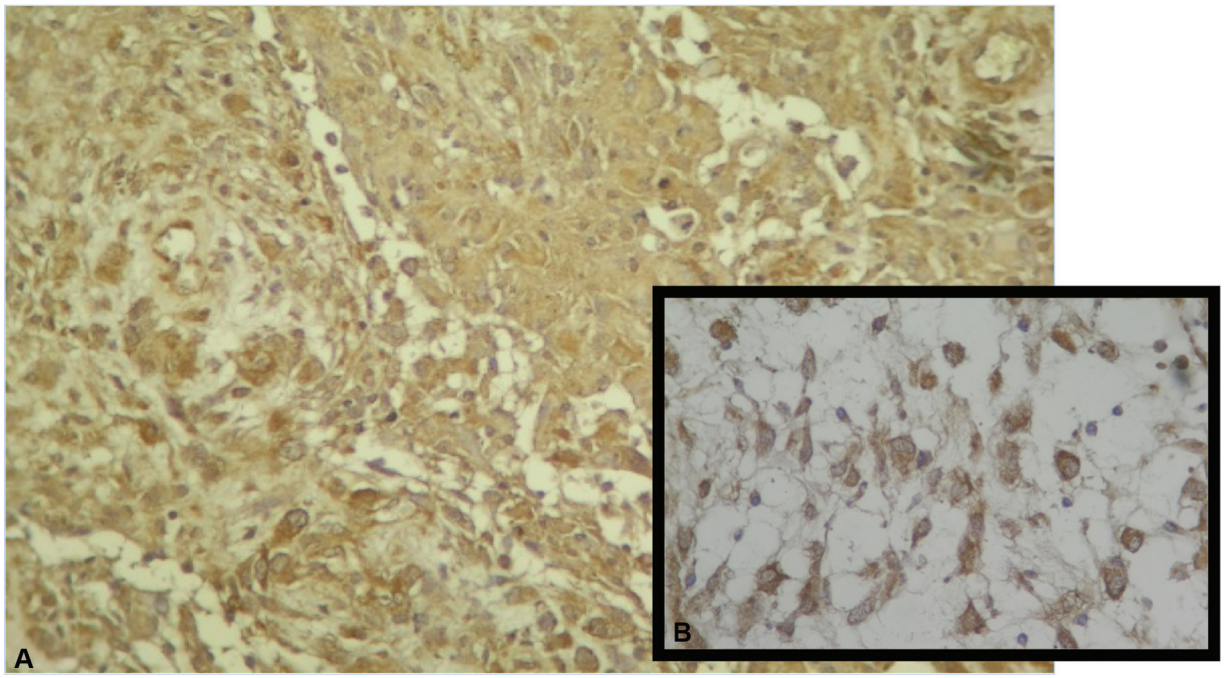


Fig. 3 Transforming growth factor beta 2immunoreactivity in tumor (GBM) tissue. (**A**) x200, (**B**) x400.

apart from the Smads, the signal transduction mechanism of these pathways at the molecular level is not fully known.

Transforming growth factor beta superfamily members act by activating transmembranic receptors. It, then, initiates the flow of regulatory SMAD proteins located from the cytoplasm to the nucleus, acting as transcriptional regulators.

Transforming growth factor beta receptors in glycoprotein structure of TGF-β superfamily members are classified as type I (TßR-I; 55kDa), type II (TßR-II; 70–100 kDa), and type III (TßR-III; 200–400 kDa). Types I and II are responsible for signal transmission. Seven type-I receptors (ALKs 1–7) and 5 type-II receptors (Act-IIA, Act-IIB, BMPR-II, AMHR-II, TBR-II) were detected in the human genome.

Transforming growth factor beta and activins bind directly to type-II receptors first, and then these are activated. Next, the phosphorylation of SMAD proteins, which provides

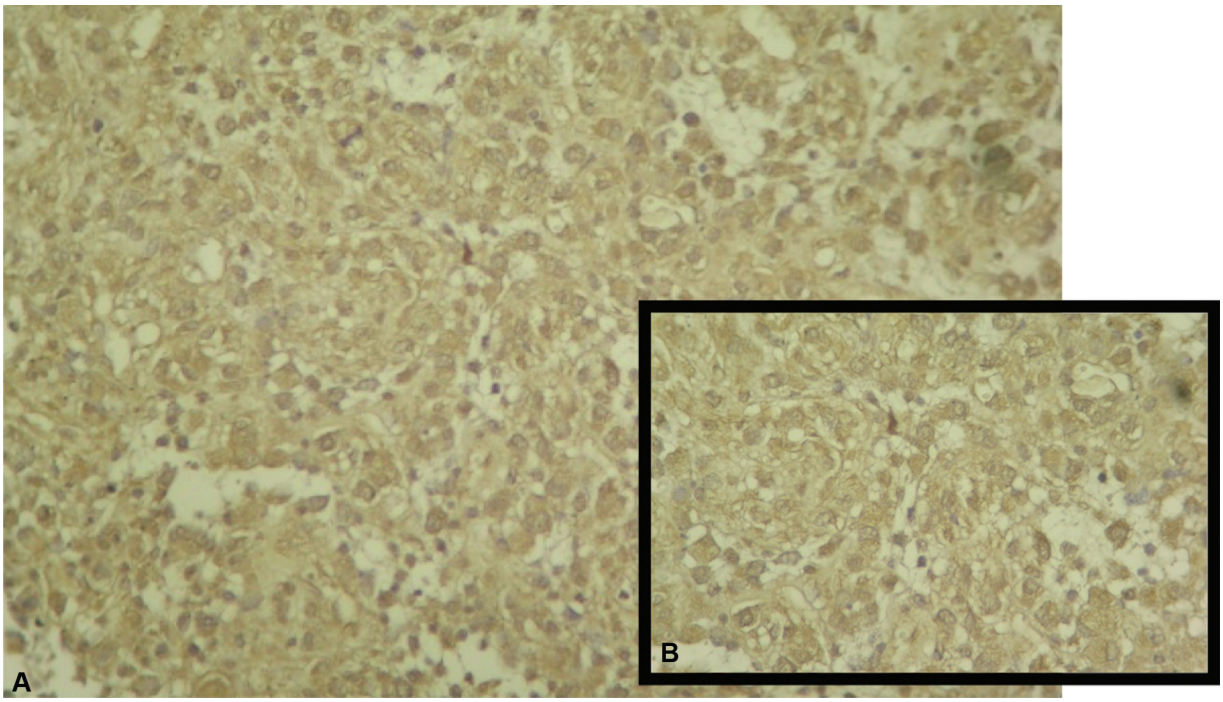


Fig. 4 Transforming growth factor beta 3immunoreactivity in tumor (GBM) tissue. (**A**) x200, (**B**) x400.

Table 2 Statistical immunoreactivity values of the transforming growth factors beta family and Smad receptors

RECEPTOR COMPARISON	*P-value*
TGF-β1 - TGF-β2	$P < 0.001^*$
TGF-β1 - TGF-β3	$P > 0.05$
TGF-β2 - TGF-β3	$P < 0.001$-
Smad 1/2/3 - Smad 6	$P > 0.05$
Smad 1/2/3 - Smad 7	$P > 0.05$
Smad 6 - Smad 7	$P < 0.001^*$

**p-value* < 0.001 is statistically significant.

the signal flow from cytoplasm to the nucleus, is achieved through type-I receptors.

Another receptor of the TGF-β family that mediates signal transduction is the type-III receptor. Type-III receptors meet extracellular ligands to reach signal receptors (types I and II).

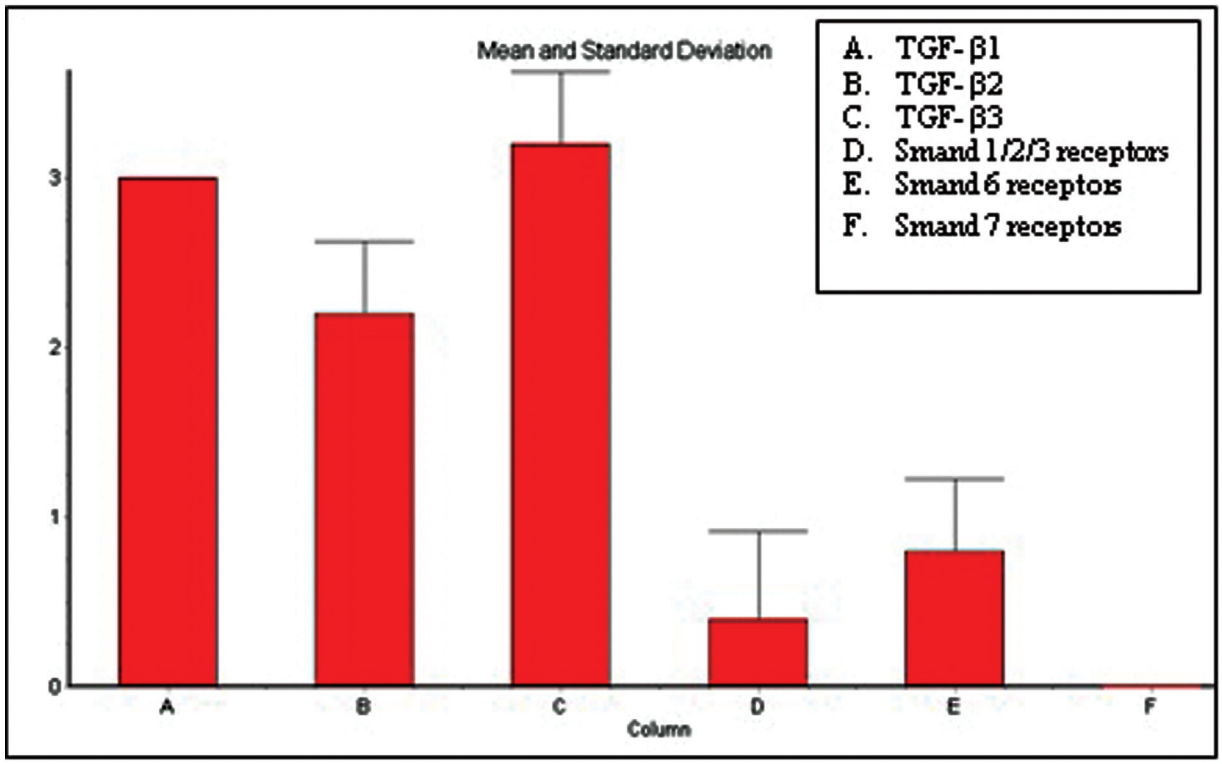
The Smad family proteins were first identified as substrates for type-I receptor kinases. They play a central role in transmitting the receptor signal to target genes in the nucleus. Approximately 10 Smad proteins have been identified to date. The Smad family is classified into three subgroups according to its structural and functional characteristics. The first group, which includes Smads 1, 2, 3, 5, 8 members, is called the "receptor-regulator Smad" (R-Smad). Smads 1, 5, and 8 interact specifically with bone morphogenetic protein (BMP) type-I receptors. Smads 2 and 3 interact with the receptors of activin and TGF-β. The second subgroup is the "common agent-Smad" (common-Smad = co-Smad). Co-Smads found in vertebrae are only Smad 4.

Co-Smads form heterooligomers with R-Smads and activate signal transduction to the nucleus. In vertebrae, the third group is the "inhibitory smad" proteins, including Smads 6 and 7. The only known function of Smads in this group is that R-Smads inhibit the signal activity. Smad 6 inhibits BMP signaling. Smad 7 inhibits both TGF-β and BMP signaling. It was observed that the levels of Smad 6 and 7 proteins act as negative feedback control of the function of Smads in response to BMP, activin, or TGF-β increase.[9]

Sasaki et al. showed active and latent forms of both TGF-β1 and TGF-β2 in malignant glioma cell culture. However, furthermore, the possible antitumoral activity of the TGF-β signal in gliomas has not been demonstrated[10]. On the contrary, evidence has been found that TGF-β expression in malignant brain tumors causes tumor cells to proliferate, migrate and invasion in the survival, while providing an advantage to tumor cells by causing angiogenesis and immune suppression.

Microvascular proliferation and necrosis are found in these aggressive and highly malignant tumors. Glial fibrillary acidic protein (GFAP) is undoubtedly the most important marker in neoplastic astrocytes, and many cells, including most aggressive GBMs, are stained with GFAP staining. Vimentin and fibronectin expressions are also frequent, but less specific.[11]

The K_i-67 nuclear antigen is a proliferation marker that is secreted only from proliferating cells. It has been shown that cell proliferation is particularly closely related to the S (synthesis) phase.[12,13] Quantitative K_i-67 measurements provide accurate information about the proliferation index of tumors. As a result of the studies on this subject, it has been revealed that it is closely related with cancer prognosis.[14]



Graphic 1 Average and standard deviation values of immunoreactivities of TGF-βs family and Smad receptors.

Epithelial-mesenchymal change is seen in the management of morphogenesis in multicellular organisms. This process also plays a role in the development of fibrosis and carcinoma. Well-preserved pathways play a role on this. As the epithelial cells lose their polarity, embryonic mesenchymal cell formation is observed with the loss of cell connections, deterioration of the cytoskeleton, and change of organelles. The loss of vimentin and e-cadherin is held responsible for this situation. Epithelial-mesenchymal transition development is followed by pathways associated with the tyrosine kinase surface receptor, TGF-β signaling pathways, influence of Smad proteins, and GTPase activity. In

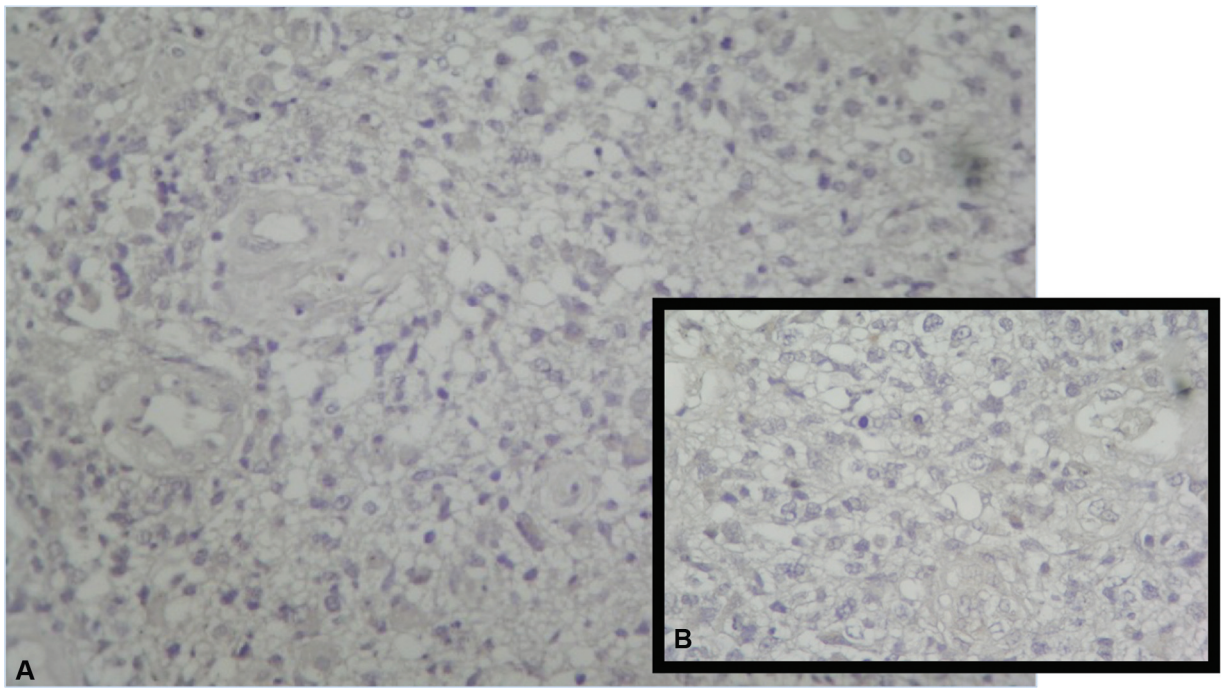


Fig. 5 Smad1/2/3 immunoreactivity in tumor (GBM) tissue (**A**) × 200, (**B**) × 400.

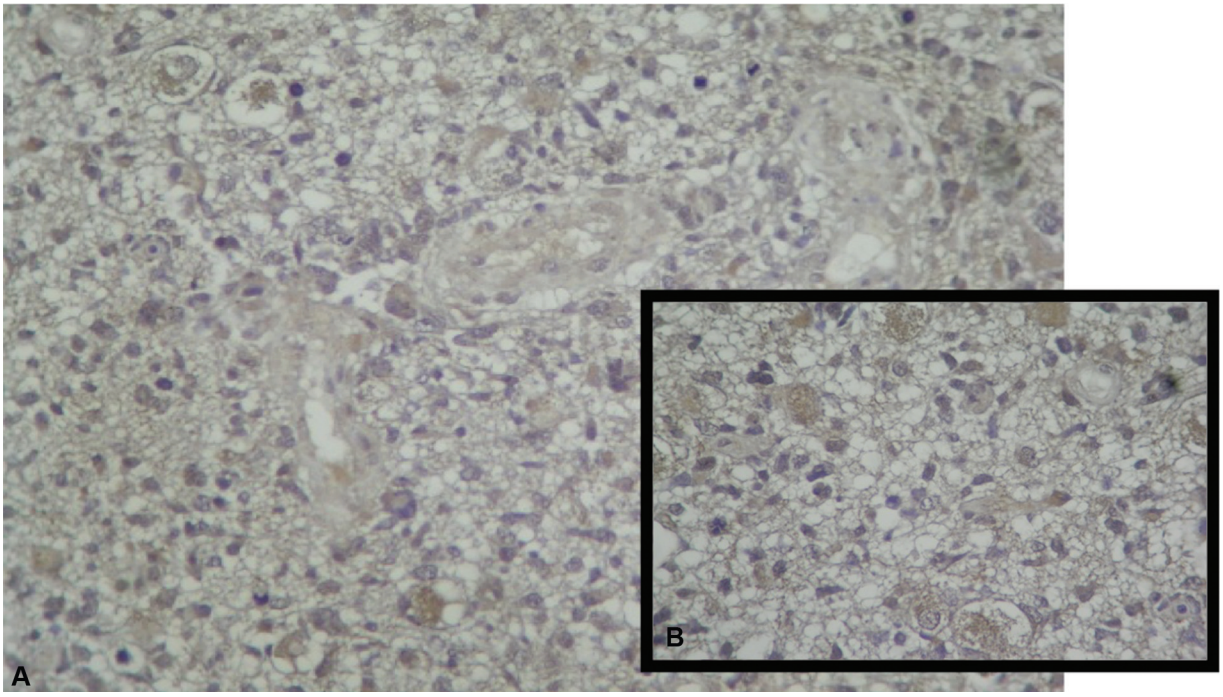


Fig. 6 Smad 6 immunoreactivity in tumor (GBM) tissue. (**A**) × 200, (**B**) × 400.

particular, TGF activity triggers the transcription of intracellular Smad family members by acting on type-I and type-II receptors. Epithelial cell plasticity and dedifferentiation are important steps in carcinoma development for invasive and metastatic tumor morphogenesis. Studies on the TGF family and activation on their receptors are particularly limited. Transforming growth factor family members are known to be important in cell proliferation, differentiation, and migration. Since it is thought that TGF family members may have roles in epithelial tumors—both primary and metastatic tumors—it is thought that knowing which receptors they activate, and which other pathways are activated after the activation of these receptors in the cell will be important in personalized treatments and effective tumor treatment. Since the roles of the TGF family and receptors in the EMT in metastatic cancer cells are also known, it will be important

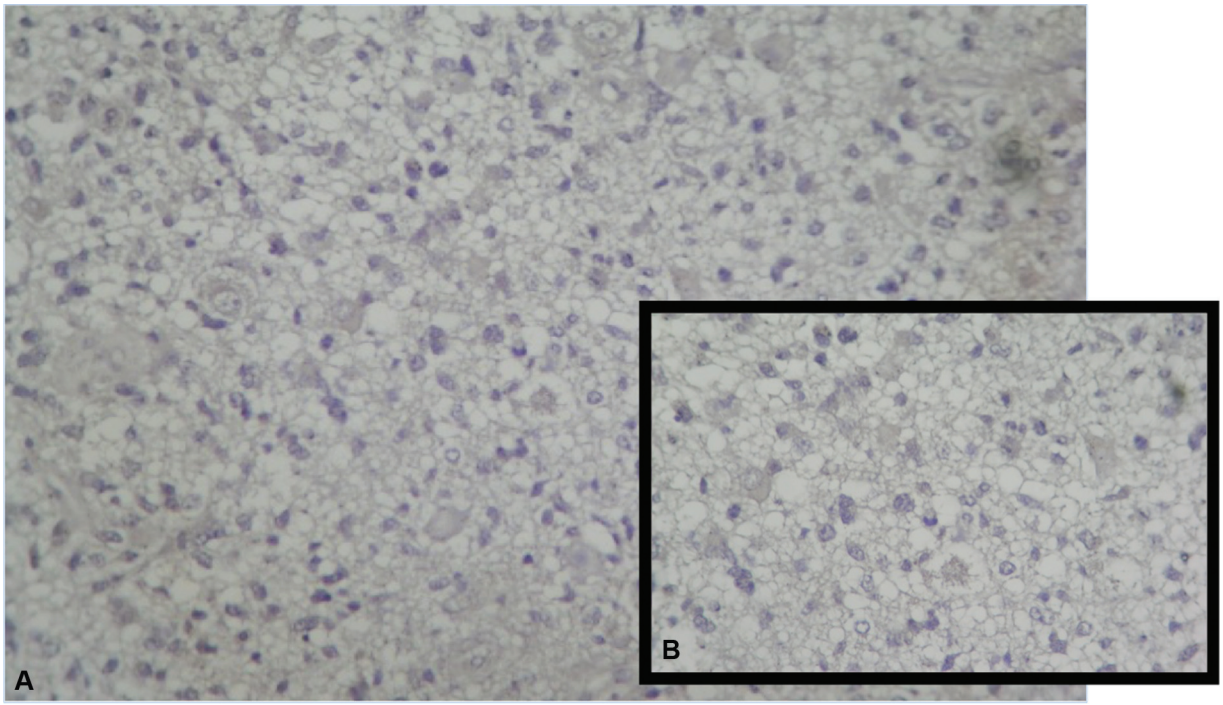


Fig. 7 Smad 7 immunoreactivity in tumor (GBM) tissue (**A**) × 200, (**B**) × 400.

to evaluate such patient groups in terms of the control mechanisms of the primary tumor and the tendency to metastatic tumor development. Although each of these pathways is the target of detailed studies, studies have been performed on its effect on prognosis and resistance to chemotherapy.[15]

High-grade gliomas tend to show severe invasion. Tumor relapse occurs frequently ($>90\%$) at the tumor margins, even after total tumor resection and many surgical procedures. This invasive phenotypic feature of GBM is thought to be due to the activation of some surface receptors, including receptor tyrosine kinase (RTKs), G-protein-coupled receptor (GPCRs), integrins, tumor necrosis factor (TNF), cytokine receptors, protein tyrosine phosphatase receptors, and the TGF-β family. On the other hand, locally released TGF is thought to play an active role in metastasis formation with phosphorylated Smad 2.

In the basal part, Smads are found as homooligomers. Type-I receptor kinases phosphorylate specific Smads after ligand activation of the receptor complex. The phosphorylated Smads then combine with Smad 4 and are transported to the cell nucleus. These complexes can be found alone or in conjunction with the DNA-binding subunit in the core and activate target genes by binding to specific promoter elements.

Nuclear translocations of Smads activated by the receptor occur through the phosphorylation induced by agonists and the binding kinetics with Smad 4. Smad 4 translocates into the cell nucleus in response to TGF-β and BMP, and translocation occurs in the presence of Smad 1 and Smad 2. Receptor-activating Smads bind to Smad 4 in the cytoplasm and transport it into the cell nucleus.

Various forms of negative regulation of cell proliferation, such as arresting the cell at the G_1 stage, increasing terminal differentiation or activation of cell death mechanisms, are the effects of TGF-β on target cells. It is thought that susceptibility to cancer or cancer may occur due to disruption of TGF-β signaling.

The fact that especially TGF-β1 and TGF-β3 immunoreactivities are high in the patient samples, in GBM cases, the tumor cells release these two TGF proteins, and as the receptor, Smad 6, which is the inhibitor receptor, is secreted more than Smad 7, suggesting that it has a protective effect in the tissue. Smad 6 and Smad 7 are inhibitors of signal transduction with R-Smads. In the absence of expression, Smad 6 inhibits BMP and partially TGF-β signal transduction. Smad 7 can also inhibit TGF-β and BMP signal transduction. On the other hand, Smad 1, 2, and 3 proteins phosphorylated by type-I receptor were found to be positive in these samples, and they were phosphorylated in some patient groups and initiated intracellular signaling; however, it results in some patient groups not being activated much.

Smads, the most important mediators of the TGF-β family of signal transduction, are exposed to different types of regulation mechanisms to complete and adapt the signal transduction according to the state of the cell. In cancer, the TGF-β signal transduction network is damaged by Smad 2, and Smad4/DPC4 mutations. Smad4/DPC4 has been identified as a candidate tumor suppressor gene on chromosome 18q21. Since TGF family members are activated with type-I and type-II surface receptors other than Smad receptors, the observation of positively stained TGFs, as well as the fact that Smad family members are less stained, TGF-β family members can trigger other receptors in addition to Smad protein in these patient samples and its effect suggests that it can show it that way. Precilinic data and experimental studies show that treatments targeting TGF-β are of great value in the treatment of gliomas.[1]

The observation of TGF-β2 immunoreactivity in both tumor cells and brain connective tissue showed that it is not only tumor-specific but also secreted from the cortex, suggesting that it is less important to evaluate it clinically in this patient group compared with TGF-β1 and TGF-β3.

Our study has potential limitations. One limitation is its retrospective design, and the other limitation is that this is a single-center study.

Conclusion

As a result of the histochemical and immunohistochemical staining of patients with high grade primary brain tumor (glioblastoma multiforme), it is observed that the expression of TGF-β1 and TGF-β3 proteins increases. Among the inhibitory receptors, Smad 6 is secreted more than Smad 7, suggesting that Smad 6 has a protective role in the tissue. Smad 1, 2, and 3 receptors were also partially increased in some patients and not at all in others. The intensive immunohistochemical staining of TGF-β family proteins activated by type-I and type-II receptors and the partial staining of the Smad family suggest that the TGF-β family can also act via a receptor mechanism other than Smad receptors.

Therefore, in addition to the investigation of Smad receptors, receptors such as Shc-GBR2, SARA, and Ras-Erk1/2 should also be examined, as they are important to regulate patient-specific chemotherapy regimens and immunotherapies for treatment and prognosis.

Conflict of Interests

The authors have no conflict of interests to delcare.

References

1 Joseph JV, Balasubramaniyan V, Walenkamp A, Kruyt FA. TGF-β as a therapeutic target in high grade gliomas - promises and challenges. Biochem Pharmacol 2013;85(04):478–485. Doi: 10.1016/j.bcp.2012.11.005

2 Yan YR, Xie Q, Li F, et al. Epithelial-to-mesenchymal transition is involved in BCNU resistance in human glioma cells. Neuropathology 2014;34(02):128–134. Doi: 10.1111/neup.12062

3 Massagué J TGFbeta in Cancer. Cell 2008;134(02):215–230. Doi: 10.1016/j.cell.2008.07.001

4 Gout S, Huot J. Role of cancer microenvironment in metastasis: focus on colon cancer. Cancer Microenviron 2008;1(01):69–83. Doi: 10.1007/s12307-008-0007-2

5 Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol 2000;182(03):311–322. Doi: 10.1002/(SICI)1097-4652(200003)182:3<311:AID-JCP1>3.0.CO;2-9

6 Louis DN, Holland EC, Cairncross JG. Glioma classification: a molecular reappraisal. Am J Pathol 2001;159(03):779–786. Doi: 10.1016/S0002-9440(10)61750-6

7 Barutcuoglu M, Umur AS, Vatansever HS, et al. TGF-βs and Smads activities at the site of failed neural tube in the human embryos. Turk Neurosurg 2013;23(06):693–699. Doi: 10.5137/1019-5149.JTN.9428-13.0
8 Platten M, Wick W, Weller M. Malignant glioma biology: role for TGF-beta in growth, motility, angiogenesis, and immune escape. Microsc Res Tech 2001;52(04):401–410. Doi: 10.1002/1097-0029(20010215)52:4<401:AID-JEMT1025>3.0.CO;2-C
9 Rich JN. The role of transforming growth factor-beta in primary brain tumors. Front Biosci 2003;8:e245–e260. Doi: 10.2741/992
10 Sasaki A, Naganuma H, Satoh E, et al. Secretion of transforming growth factor-beta 1 and -beta 2 by malignant glioma cells. Neurol Med Chir (Tokyo) 1995;35(07):423–430. Doi: 10.2176/nmc.35.423
11 Bruce JN, Kennedy B, Shepard RC. Glioblastoma multiforme. Med Oncol 2009;5(08):
12 Gasparini G, Boracchi P, Verderio P, Bevilacqua P. Cell kinetics in human breast cancer: comparison between the prognostic value of the cytofluorimetric S-phase fraction and that of the antibodies to Ki-67 and PCNA antigens detected by immunocytochemistry. Int J Cancer 1994;57(06):822–829. Doi: 10.1002/ijc.2910570610
13 Vielh P, Chevillard S, Mosseri V, Donatini B, Magdelenat H. Ki67 index and S-phase fraction in human breast carcinomas. Comparison and correlations with prognostic factors. Am J Clin Pathol 1990;94(06):681–686. Doi: 10.1093/ajcp/94.6.681
14 Burcombe R, Wilson GD, Dowsett M, et al. Evaluation of Ki-67 proliferation and apoptotic index before, during and after neoadjuvant chemotherapy for primary breast cancer. Breast Cancer Res 2006;8(03):1–10
15 Thiery JP. Epithelial-mesenchymal transitions in development and pathologies. Curr Opin Cell Biol 2003;15(06):740–746. Doi: 10.1016/j.ceb.2003.10.006

What a Neurosurgeon Should Know About the Endolymphatic Sac: Part 2 – Diagnosis and Management of the Endolymphatic Sac Tumors

O Que um Neurocirurgião Deve Saber Sobre o Saco Endolinfático: Parte 2 – Diagnóstico e Manejo dos Tumores do Saco Endolinfático

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Abstract

Objective This article is divided into three parts. In the second part of this review, the authors focus on describing the endolymphatic sac tumor and presenting illustrative cases.

Methods A review of previous studies, from 1957 to 2021, from basic and translational research using human and animal endolymphatic sac (ES) tissue or cells, as well as other reviews on this theme.

Results The ES is an inner ear structure, which is responsible for the homeostatic regulation, as well as endolymphatic fluid volume control, immune response etc. One of the possible alterations of the ES is the ELST, a low-grade malign neoplasm that originates from the epithelium of the endolymphatic duct and sac. The clinical presentation of the ELST includes hearing loss, tinnitus, headache, and vertigo. The

Keywords
- endolymphatic sac
- tumor
- clinic
- diagnosis
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diagnosis in the early stages is rare, given that this group of symptoms is very similar to other, more common, diseases such as the Meniere syndrome. Its diagnosis is made by computed tomography (CT), magnetic resonance imaging (MRI), immunohistochemistry, and confirmed by histopathology. However, none of these examinations are part of the pathological guidelines for ELST. The treatment for ELST in the early stages has a high rate of success.

Conclusion The ELST is a very difficult diagnosis due to its presentation. Furthermore, the interactions between ELST and the Von Hippel-Lindau disease usually result in a more aggressive condition. Despite the difficulty of the diagnosis, doing it early increases the chances of successful treatment.

Resumo

Objetivo Este artigo é dividido em três partes. Na segunda parte desta revisão, os autores focam em descrever os tumores do saco endolinfático (TSE) e apresentar casos ilustrativos.

Métodos Revisão de estudos prévios, de 1957 até 2021, de pesquisa básica até translacional usando tecidos ou células do saco endolinfático (SE) humanas e animais, além de revisões sobre o assunto.

Resultados O SE é uma estrutura situada na orelha interna, e é responsável pela regulação homeostática, controle do fluido endolinfático, resposta imune, etc. Uma das possíveis alterações do SE são os TSE, uma neoplasia de crescimento lento, com agressão local e de baixo grau, que se origina do epitélio do saco e do ducto endolinfático. A apresentação clínica do TSE se dá com perda auditiva, zumbido, cefaleia e vertigem. O diagnostico em estágios iniciais é raro devido a apresentação clínica similar a diversas outras patologias mais comuns como a Síndrome de Ménière. O diagnóstico é feito com por tomografia computadorizada (TC), ressonância magnética (RM), imuno-histoquímica e confirmada com histopatologia. Entretanto nenhum desses exames está nas diretrizes das patologias que mimetizam o TSE. O tratamento para o TSE em estágios iniciais tem uma alta taxa de sucesso.

Conclusão O TSE é uma patologia de difícil diagnostico devido a sua apresentação. Além disso, a interação entre o TSE e a doença de Von Hippel-Lindau resulta em uma condição mais agressiva da doença de maneira geral. Apesar dessa dificuldade de diagnostico, fazê-lo em estágios iniciais aumenta muito as chances de sucesso no tratamento.

Palavras-chave
- saco endolinfático
- tumores
- clínica
- diagnóstico
- tratamento
- neurocirurgia

Introduction

In the first part of this article, we studied the endolymphatic sac's (ES) microanatomy and physiology. Evidence supports the idea that the ES has a very distinctive function when compared with the structures around it, such as homeostasis regulation of the inner ear, endolymphatic fluid volume control, immune response, elimination of inner ear cellular debris and floating otoconia, membranous labyrinth pressure management, acid/basic transport, and secretion of substances.[1–11]

The ES, despite being only 3 mm in diameter, does not have a very variable location inside the inner ear.[8,12] Almost every alteration in this structure can cause a massive problem to hearing, including hearing loss.[13] One of these possible problems is the endolymphatic sac tumor (ELST), a slow-growing, locally aggressive, low-grade malign neoplasm that originates from the epithelium of the endolymphatic duct and sac.[14]

In this review, our aim is to elucidate the clinical presentation, diagnosis, and treatment of the ELST.

Methodology

This article is divided into three parts. In this second part, we review the ELSTs and present illustrative cases. We focused on evidence collected from 1957 to 2021, including basic and translational researches using human and animal ES tissue or cells, as well as previous reviews about the subject, using the terms individually and combined: *Endolymphatic sac tumor*, *Clinic*, *Diagnosis*, *Treatment*, *Neurosurgery*. Literature inclusion criteria were articles in written English, including individual case studies and long-term follow-up studies; the exclusion criteria were duplicate studies with high

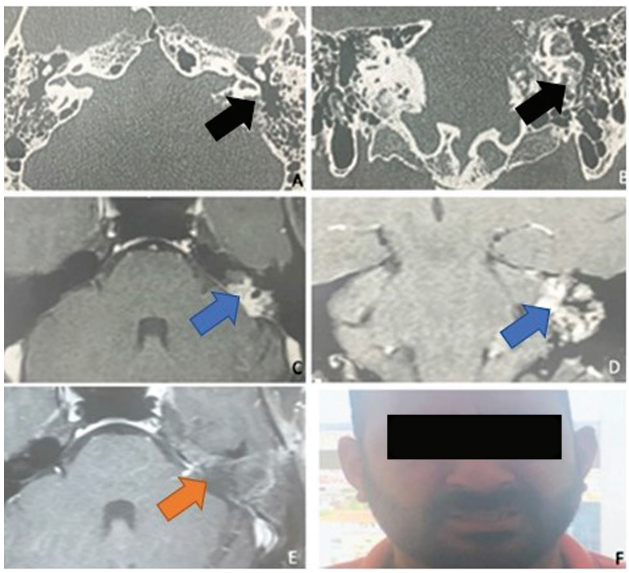

Fig. 1 Case 1, axial (A) and coronal (B) CT scan of the temporal bone in the bone window, showing destruction on the petrous portion of the temporal bone. Axial (C) and coronal (D) MRI scans of the T1 with gadolinium showing tumor inside the mastoid portion of the temporal bone, with involvement of the Trautmann triangle's dura mater. MRI of the T1 with gadolinium 3 months after surgery, showing total resection of the lesion (E) with facial nerve preservation (F). Black arrow: expansive lesion with erosion of the temporal bone's petrous portion. Blue arrow: tumor seen in the MRI scan. Orange arrow: late postoperation exam showing complete tumor resection.

similarity and articles that not fit into the including criteria. First, we briefly reviewed the basic aspects of the ELST, followed by a more detailed explanation of its clinical presentation, diagnosis, and treatment. This study may provide a basis for planning early-stage diagnostic guidelines.

Results

Illustrative Cases

Case 1

A patient with conduction hyperacusis in the left ear for 6 months came to our clinic with a cranial CT showing left temporal lobe bone erosion, and an MRI with gadolinium suggesting ESLT. A transmastoid approach was used to make a full resection of the tumor (►**Fig. 1**). Histopathology confirmed the ELST, and the patient do not have a tumoral recurrence during 6 years of attendance (►**Fig. 2**).

Case 2

A 37-year-old woman with right ear vertigo and deafness for 4 years. In the last few months, she'd noticed otorrhagia in the same ear. Developed facial paralysis (HB 3) and right symmetry in the last month (►**Fig. 3**,**4**,**5**,**6**).

Basic Aspects of the ELST

The ELST is an aggressive, slow-growing, with low-grade malignancy that originates from the epithelium of the endolymphatic duct and sac.[14] In 1957, the term *ceruminoma* was first coined to the adenomas and adenocarcinomas of the external auditory canal. However, the origin of middle and inner ear adenomas is still unclear and, consequently, the origin of ELST is still in debate. Some authors support that it originates from aberrant ceruminous glands, while others postulate that the tumors arise from native middle ear mucosa.[14,15]

It is known that 11% of the patients with the Von Hippel-Lindau (VHL) disease will develop ELST.[16,17] Thus, the epithelium of the ES can produce an aggressive papillary lesion (APL); ELST may also present a follicular pattern (AFL) on light microscopy.[14]

The APL refers to a papillary protuberance with arranged cuboidal or low columnar cells. On the other hand, the AFL is represented by cists full of thyroid follicles proteinaceous debris, although thyroglobulin stains were not found. Some ELST may have both alterations.[18]

According to the literature, ELST is cytokeratin and vimentin-positive, and the majority will be S-100 positive. Furthermore, ELST is chromogranin negative, which can differentiate them from the paraganglioma, and transthyretin negative, which distinguishes them from the choroid plexus tumor. Also, they are thyroglobulin negative, unlike metastatic thyroid cancer.[19,20]

Clinical Presentation

The most common symptom observed by Poletti[21] in his study was unilateral deafness. This hearing loss can be explained by the association with the Meniere disease.[22] Additionally, the most common symptoms include tinnitus and vertigo.[19]

The ELST originates at the temporal bone's posteromedial aspect, and from there it can spread posteriorly to the cerebellopontine angle.[14,19] This expansion can cause brainstem compression and, consequently, several neurological deficits.[14,19,20] Another possible tumor spread is the lateral way which can affect the facial nerve or mimic middle ear infection symptoms.[14,19] The jugular foramen syndrome (glossopharyngeal neuralgia, hypoglossal paralysis, and motor disturbances) or cerebellopontine angle syndrome (hearing loss, facial paralysis, and balance disturbance) are both also possible impairments.[19] Death only happened in cases of vascular issues and high intracranial pressure.[14]

One of the biggest challenges in the ELST is the distinction from the Meniere disease.[22] The clinic presentation of this pathology is tinnitus, unilateral hearing loss, aural fullness, and vertigo,[9] which mimics the symptoms of the ELST, since it create a barrier for the endolymph reabsorption as it grows, producing excess fluid and secondary hydrops (SNHL).[14]

Another important association for ELST is the Von Hippel-Lindau (VHL) disease, which is an autosomal-dominant, multisystem disorder characterized by cerebellar hemangioblastomas, retinal angiomas, renal or pancreatic cysts, renal cell carcinoma, pheochromocytomas, and other visceral tumors, according to Wick et al.[14] Despite having no clinical mimetics, 11% of the patients with VHL will develop ELST, and 30% of those will have severe impairment with bilateral lesions.[14,16,17] The average age in which ELST patients

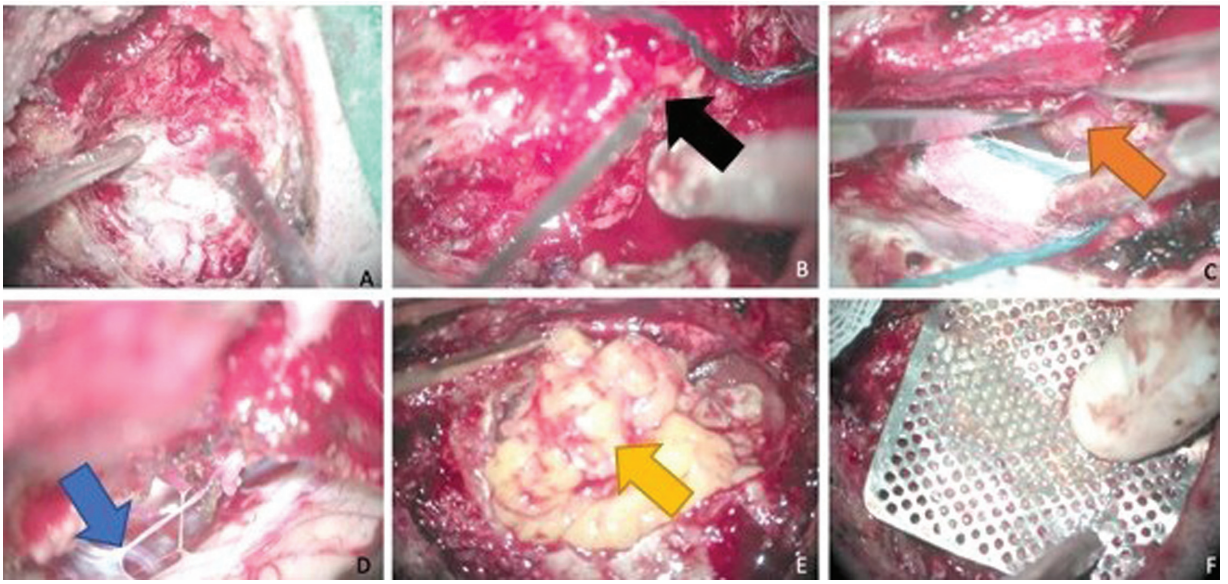

Fig. 2 Case 1, intraoperative vision. The mastoidectomy is performed (A). The mastoid portion of the facial nerve is identified through anatomic parameters and facial nerve stimulation, in cases where the nerve is not in the bone canal (B). The Trautmann triangle is incised, and the tumor is identified (C). Removal of the tumor along with the Trautmann triangle dura mater (D). The mastoid cavity is sealed with abdominal fat (D). Before that, the Eustachian tube is sealed with muscle. The titanium mesh position in a steady way, making pressure over the fat is crucial to avoid cerebrospinal fluid (CSF) leak. Thereunto, it is important to do a bone flat fixation with screws into the temporal bone edges (F). Black arrow: mastoid segment of the facial nerve being localized with 0.05 mA electrical stimulus. Orange arrow: tumor is adherent to the dura of the Trautmann triangle. Blue arrow: anterior inferior cerebellar artery (AICA). Yellow arrow: abdominal fat is used to avoid CSF leak.

without VHL express symptoms was 52.5 years, whereas in the group with VHL, the average was 31.3 years.[23,24] Thus, ELST in patients with VHL can occur in younger people and more aggressively.

Diagnosis

Two of the most important exams to neurosurgery, computed tomography (CT) and magnetic resonance imaging (MRI) scans, also make themselves indispensable for the diagnosis of ELST.[14] Contrast CT presents with enhancement of soft-tissue masses with bone erosion over the ES. In late presentations, intratumor and kidney-shaped calcifications are seen.[14,25,26]

Examinations through MRI also show the heterogeneous focus of low and high signal intensity on T1 and T2 imaging. The hyperintense areas on T1 represents intraparenchymal hemorrhage and the hypointense reflect residual bone or prominent calcification. With contrast the image often shows heterogeneous patterns.[14,25,26]

Regardless of the CT and MRI scans, the differential diagnosis is still challenging. Paraganglioma (glomus jugular or glomus tympanicum), choroid plexus tumor, metastasis, eosinophilic granuloma, meningioma, arachnoid granulation, aneurysmal bone cyst, or a primary bone tumor are some the pathologies that can be seen with similar patterns to the ELST.[14,26,27] However, the immunohistochemical technique is one the few that can differentiate the previously described entities.[14]

The diagnosis can be confirmed by histopathologic analysis.[22] It reveals bone and tissue infiltrations, surrounded by neoplastic lesions and fibrous core. The histopathologic difference of low and high magnification is the clear cells presentation in the higher one.[22]

In 2004, Bambakidis et al.[28] made a classification for ELST based on tumor extension. Furthermore, they suggested surgical options for each of the grades (►**Table 1**).

The patients' clinical history related to VHL must be investigated. In the absence of this data, according to Magerian et al., it is mandatory to obtain a detailed history of first-degree relatives for problems such as retinal angiomas, renal or pancreatic cysts, pheochromocytomas, or other manifestations of VHL. In the cases of suspected VHL, the patient's family must be called for genetic tests and consulting.[23]

Despite the difficult diagnosis, doing it in the early stages is crucial for better chances of total resection surgery and hearing preservation; specially in VHL patients who have an increased risk for bilateral ESLT and, consequently, total hearing loss.[28]

Treatment

The technique for removal of both sides of the dural sleeves around the ES that shows the most effective results has been called retrolabyrinthine-transdural approach (RTA) or the retrolabyrinthine posterior necrosectomy approach.

For the RTA procedure, the patient is placed supine and positioned with the head turned away from the surgeon. The patient's hair is shaved, but usually head pins aren't necessary. A facial nerve monitor is used to identify possible injuries in this structure during the procedure.

With all the preincision steps done, a mastoidectomy is performed to identify the horizontal semicircular canal and the facial nerve. Afterwards, the following structures are

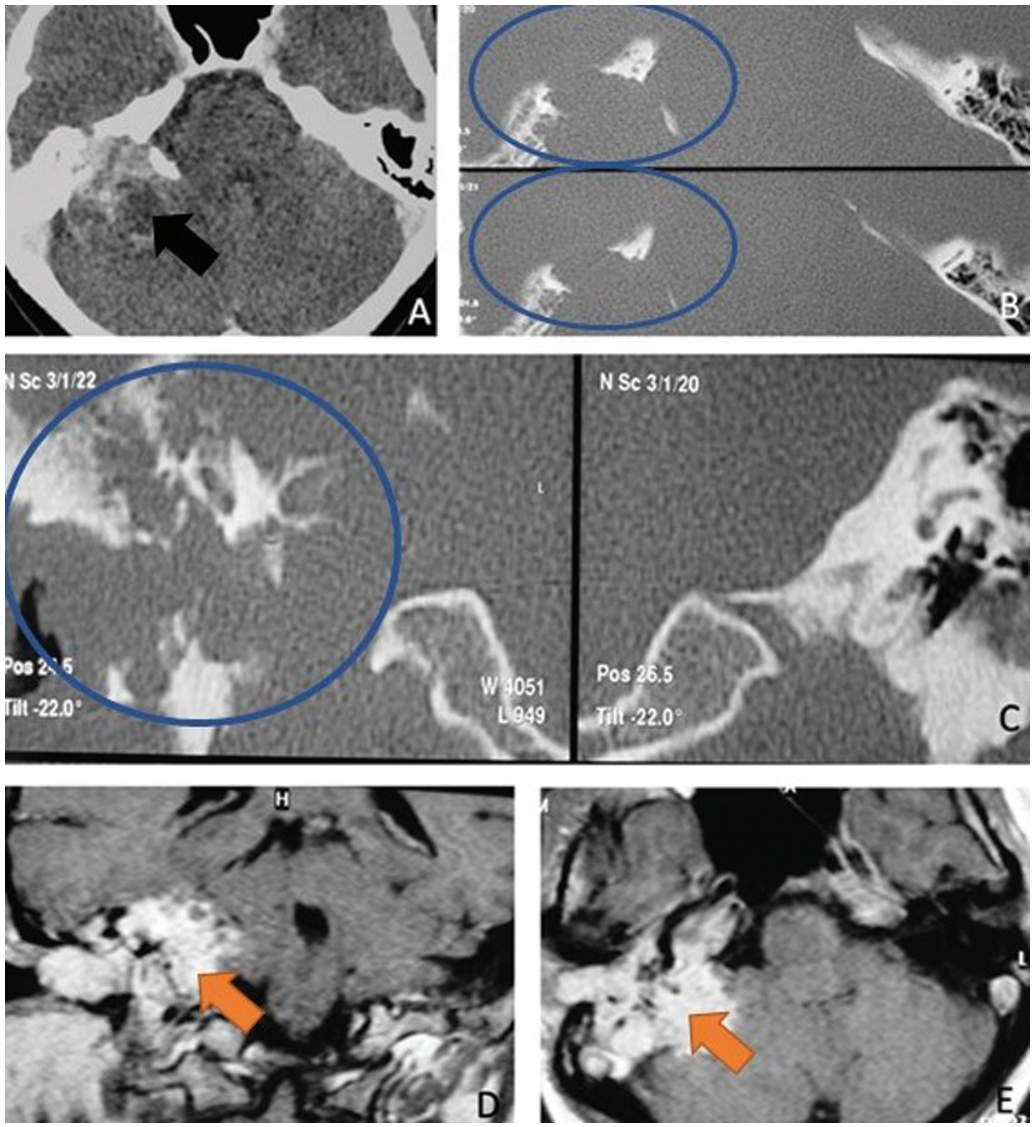

Fig. 3 Case 2, CT scan revealed a right angle cerebellopontine tumor, with erosion of the mastoid part of the temporal bone (A). The axial (B) and coronal (C) CT scans in the bone window, showing erosion and destruction of the temporal bone. Coronal (D) and axial MRI scans of the T1 with gadolinium (E) show that the tumor is occupying the mastoid part of the temporal bone with an extension on the cerebellopontine angle and external auditory canal. Black arrow: cerebellopontine angle tumor. Blue circles: bone lesion in the temporal bone petrous portion. Orange arrow: expansive lesion seen in MRI.

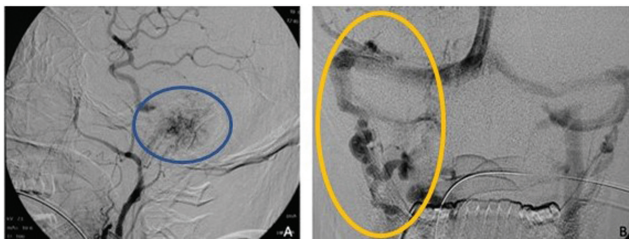

Fig. 4 Case 2, Angiography showing tumoral nutrition by the external carotid artery branches that were embolized during this procedure (A). The right side of the Sigmoid sinus was obstructed by the tumor on the preoperatory period (B). Blue circle: expansive lesion after embolization. Yellow circle: venous flow alteration through expansive lesion.

skeletonized: the tegmental dura, the sinodural angle, and the jugular bulb. Normally, after those steps, the ES and the tumor can be seen.[23]

When the ELST is identified, the endolymphatic duct is followed with a diamond burr and the tumor is resected. If the posterior semicircular canal is injured, it can be sealed quickly with bone wax; however, lesions in this structure need to be avoided as much as possible, to decrease post-op complications.[23]

After the tumor removal, the bone around the tumor must be extracted with a margin of 0.5 cm, as the sac and duct are removed en bloc. The antrum is then sealed with bone wax and the dura with abdominal fat.[23]

In two studies,[29,30] with a total of 9 patients affected by grade I tumors, the RTA uniformly resulted in hearing

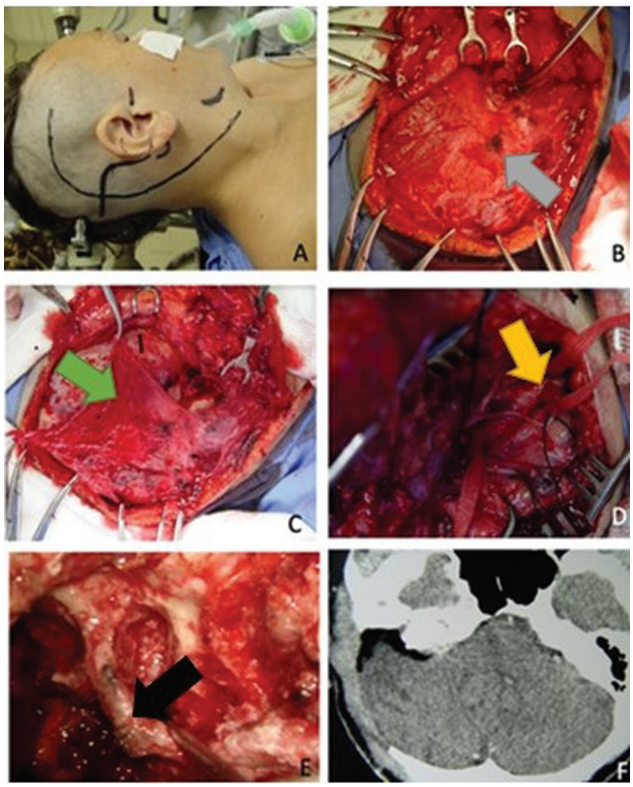

Fig. 5 Case 2, a type C Fisch approach was chosen (A). The temporoparietal fascia and the temporal muscle are identified and individualized for pedicular flap preparation on the preoperatory period (B and C). The cervical neurovascular structures are dissected and individualized for proximal control over the carotid artery (D). After the tumoral resection, a skeletonized intrapetrous carotid artery is observed (E). A CT scan immediately postoperatory, showing a total tumor resection (F). Gray arrow: internal auditory canal. Green arrow: pedicled muscle flap. Yellow arrow: isolated carotid artery. Black arrow: portion of the skeletonized petrous carotid.

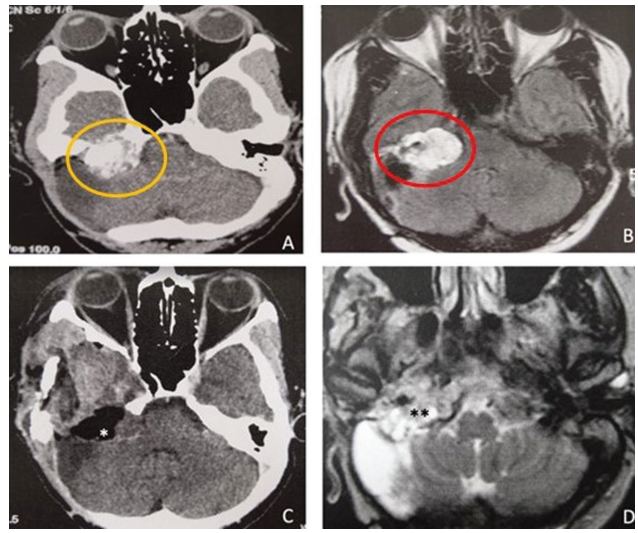

Fig. 6 Case 2, a CT scan with contrast two years after surgery (A) and an axial MRI scan of the T1 with gadolinium (B) revealed a tumoral relapse at the petrous apex, which was resected with a new surgery through the middle fossa approach and anterior necrosectomy. Postoperatory showed tumor resection (C). Three years after the last surgery a new relapse occurs on the jugular tubercle, and the tumor is resected again with another surgery. Nine years after the diagnosis the patient succumbed to the disease due to the metastatic dissemination in both lungs. Yellow arrow: tumor seen on CT scans. Red arrow: tumor seen on MRI scans.

preservation and no signs of recurrence, with follow-ups ranging from 6 months to 8 years.[23]

The translabyrinthine approach, concomitant with the RTA, is required in the cases with labyrinthine invasion, often seen in patients with poor or unserviceable hearing.[23] For patients with unresectable tumors or cases in which surgery was deemed inappropriate, stereotactic radiotherapy (SRS) using gamma knife seems to be useful in the tentative of delaying a tumor growth.[23]

Table 1 Surgical options for EST

Grade	Tumor Extent	Surgical option	Consequence
I	Confined to temporal bone, middle ear cavity, and/or external auditory canal	Retrolabyrinthine-transdural approach	Hearing preservation
II	Extension into posterior fossa	Extended retrolabyrinthine-transdural approach	Hearing preservation
		Approach with labyrinthectomy	Deafness
III	Extension into posterior fossa and middle cranial fossa	Subtemporal craniotomy with petrosectomy	Deafness
IV	Extension to clivus and/or sphenoid wing	Staged anterior and posterior fossa techniques	No mandatory consequences

Note: Adapted from Bambakidis NC, Megerian CA, Ratcheson RA. Differential grade of Endolymphatic Sac Tumor extension by virtue of von Hippel-Lindau disease status. OtolNeurotol. 2004;25:773–81.

Conclusion

The diagnosis of ELST is very difficult, since its early stages present very similar to other more common diseases, such as the Meniere syndrome. Furthermore, the interaction of the ELST and VHL disease results in an even more complicated condition in all terms, represented by its clinical presentation and challenging curative treatment.

Despite this difficulty, early diagnosis increases the chances of successful treatment in terms of hearing preservation, complete tumor resection, and lower mortality rates.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1 Kim SH, Nam GS, Choi JY. Pathophysiologic Findings in the Human Endolymphatic Sac in Endolymphatic Hydrops: Functional and Molecular Evidence. Ann Otol Rhinol Laryngol 2019;128 (6_suppl):76S–83S

2 Altermatt HJ, Gebbers JO, Müller C, Arnold W, Laissue JA. Human endolymphatic sac: evidence for a role in inner ear immune defence. ORL J Otorhinolaryngol Relat Spec 1990;52(03):143–148

3 Arnold W, Altermatt HJ, Arnold R, Gebbers JO, Laissue J. Somatostatin (somatostatinlike) immunoreactive cells in the human inner ear. Arch Otolaryngol Head Neck Surg 1986;112(09): 934–937

4 Arnold W, Altermatt HJ, Gebbers J-O, Laissue J. Secretory immunoglobulin A in the human endolymphatic sac. An immunohistochemical study. ORL J Otorhinolaryngol Relat Spec 1984;46(06): 286–288

5 Harris JP. Immunology of the inner ear: evidence of local antibody production. Ann Otol Rhinol Laryngol 1984;93(2 Pt 1):157–162

6 Harris JP. Immunology of the inner ear: response of the inner ear to antigen challenge. Otolaryngol Head Neck Surg 1983;91(01): 18–32

7 Kawauchi H, Lim DJ. Immunocompetent cell distribution in the endolymphatic sacs of normal baboons and rats. Otolaryngol (Sunnyvale) 1989;157(01):39–47

8 Lundquist PG. Aspects on endolymphatic sac morphology and function. Arch Otorhinolaryngol 1976;212(04):231–240

9 Mori N, Miyashita T, Inamoto R, et al. Ion transport its regulation in the endolymphatic sac: suggestions for clinical aspects of Meniere's disease. Eur Arch Otorhinolaryngol 2017;274(04): 1813–1820

10 Tomiyama S, Harris JP. The endolymphatic sac: its importance in inner ear immune responses. Laryngoscope 1986;96(06):685–691

11 Tomiyama S, Harris JP. The role of the endolymphatic sac in inner car immunology. Acta Otolaryngol 1987;103(01):182–188

12 Ammirati M, Spallone A, Feghali J, Ma J, Cheatham M, Becker D. The endolymphatic sac: microsurgical topographic anatomy. Neurosurgery 1995;36(02):416–419

13 Cooper MW, Kaylie DM. Is Endolymphatic Sac Surgery Beneficial For Meniere's Disease? Laryngoscope 2020;130(12):2738–2739

14 Wick CC, Manzoor NF, Semaan MT, Megerian CA. Endolymphatic sac tumors. Otolaryngol Clin North Am 2015;48(02):317–330

15 Johnstone JM, Lennox B, Watson AJ. Five cases of hidradenoma of the external auditory meatus: so-called ceruminoma. J Pathol Bacteriol 1957;73(01):421–427

16 Neumann HP, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. Lancet 1991;337(8749):1052–1054

17 Manski TJ, Heffner DK, Glenn GM, et al. Endolymphatic sac tumors. A source of morbid hearing loss in von Hippel-Lindau disease. JAMA 1997;277(18):1461–1466

18 Heffner DK. Low-grade adenocarcinoma of probable endolymphatic sac origin A clinicopathologic study of 20 cases. Cancer 1989;64(11):2292–2302

19 Devaney KO, Ferlito A, Rinaldo A. Endolymphatic sac tumor (low-grade papillary adenocarcinoma) of the temporal bone. Acta Otolaryngol 2003;123(09):1022–1026

20 Sykopetrites V, Piras G, Giannuzzi A, Caruso A, Taibah A, Sanna M. The endolymphatic sac tumor: challenges in the eradication of a localized disease. Eur Arch Otorhinolaryngol 2021;278(07): 2297–2304

21 Poletti AM, Dubey SP, Barbò R, et al. Sporadic endolymphatic sac tumor: its clinical, radiological, and histological features, management, and follow-up. Head Neck 2013;35(07):1043–1047

22 Lee KJ, Kirsch CF, Lai C, Ishiyama A. Endolymphatic sac tumor presenting with Ménière's disease. Otolaryngol Head Neck Surg 2010;142(06):915–916

23 Megerian CA, Semaan MT. Evaluation and management of endolymphatic sac and duct tumors. Otolaryngol Clin North Am 2007; 40(03):463–478, viii

24 Megerian CA, Pilch BZ, Bhan AK, McKenna MJ. Differential expression of transthyretin in papillary tumors of the endolymphatic sac and choroid plexus. Laryngoscope 1997;107(02):216–221

25 Mukherji SK, Castillo M. Adenocarcinoma of the endolymphatic sac: imaging features and preoperative embolization. Neuroradiology 1996;38(02):179–180

26 Patel NP, Wiggins RH III, Shelton C. The radiologic diagnosis of endolymphatic sac tumors. Laryngoscope 2006;116(01):40–46

27 Alkonyi B, Günthner-Lengsfeld T, Rak K, Nowak J, Solymosi L, Hagen R. An endolymphatic sac tumor with imaging features of aneurysmal bone cysts: differential diagnostic considerations. Childs Nerv Syst 2014;30(09):1583–1588

28 Bambakidis NC, Megerian CA, Ratcheson RA. Differential grading of endolymphatic sac tumor extension by virtue of von Hippel-Lindau disease status. Otol Neurotol 2004;25(05):773–781

29 Megerian CA, Haynes DS, Poe DS, Choo DI, Keriakas TJ, Glasscock ME III. Hearing preservation surgery for small endolymphatic sac tumors in patients with von Hippel-Lindau syndrome. Otol Neurotol 2002;23(03):378–387

30 Kim HJ, Butman JA, Brewer C, et al. Tumors of the endolymphatic sac in patients with von Hippel-Lindau disease: implications for their natural history, diagnosis, and treatment. J Neurosurg 2005; 102(03):503–512

Spinal Surgery in Patients with Type-1 Neurofibromatosis: A Comprehensive Review

Cirurgia da coluna em pacientes com neurofibromatose do tipo 1: Uma revisão abrangente

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Abstract

Type-1 neurofibromatosis (NF1) is a neurocutaneous syndrome classically known as peripheral NF to distinguish it from type-2 NF (central NF). Its main characteristic is the high predisposition to the growth of multiple tumors, which specially arouses the interest of spinal surgeons due to the presence of spinal cord compression and spinal deformities.

Considering this, we have performed a comprehensive review, with illustrative cases of the main manifestations of NF1, focusing on the perspective of the spine surgeon. Articles were grouped according to the following subjects: diagnosis, skeletal complications, spinal deformity, and spinal tumors. For all of them, a detailed discussion on pearls for practice was presented.

The diagnosis of NF1 is based on the presence of at least two out of seven criteria. Cutaneous findings are very common in NF1, and the most usual tumor is cutaneous neurofibroma (NFB). Plexiform neurofibromas are also found and present a high risk of becoming malignant peripheral nerve sheath tumors (MPNSTs), reducing life expectancy. Astrocytomas, especially pilocytic astrocytomas, are the most common central nervous system tumor, including in the spinal cord. Surgery is necessary to resect as much as possible without adding new neurological deficits. Spinal deformities are also commonly found (in 30–70% of the cases), potentially associated with dystrophic changes, which may result in acute and rapid progression.

In the present review, we discuss specific characteristics found in this group of patients which are of paramount importance to properly manage this challenging disease.

Keywords

- neurofibromatosis
- spinal surgery
- pilocytic astrocytomas
- dystrophic
- deformity

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Resumo

A neurofibromatose do tipo 1 (NF1) é uma síndrome neurocutânea classicamente conhecida como NF periférica para distingui-la da NF do tipo 2 (ou NF central). Sua principal característica é a alta predisposição ao crescimento de múltiplos tumores, o que desperta especialmente a interesse dos cirurgiões de coluna devido à presença de compressão medular e deformidades.

Diante disso, realizamos uma revisão abrangente, com casos ilustrativos das principais manifestações da NF1, com foco na perspectiva do cirurgião de coluna.

Os artigos foram agrupados de acordo com os seguintes assuntos: diagnóstico, complicações esqueléticas, deformidade da coluna vertebral e tumores da coluna vertebral. Para todos esses assuntos, uma discussão detalhada sobre dicas para a prática foi apresentada. O diagnóstico de NF1 é baseado na presença de pelo menos dois dos sete critérios. Achados cutâneos são muito comuns na NF1, sendo o tumor mais comum o neurofibroma cutâneo (NFB). Neurofibromas plexiformes também são encontrados e apresentam alto risco de se tornarem tumores malignos da bainha do nervo periférico (MPNSTs), reduzindo a expectativa de vida. Astrocitomas, especialmente astrocitomas pilocíticos, são os tumores mais comuns no sistema nervoso central, inclusive na medula espinhal. A cirurgia é necessária para ressecar tanto quanto possível sem adicionar novos déficits neurológicos. As deformidades da coluna também são comumente encontrada (em até 30–70% dos casos), potencialmente associada a deformidades distróficas que podem resultar em progressão aguda e rápida.

No presente artigo, discutimos características específicas encontradas neste grupo de pacientes que são de suma importância para manejar adequadamente pacientes com esta doença desafiadora.

Palavras-chave

- neurofibromatose
- cirurgia da coluna vertebral
- pilocítico astrocitomas
- distrófico
- deformidade

Introduction

Neurocutaneous syndromes comprise many diseases that concurrently affect the skin, eyes, and central nervous system (CNS), potentially affecting other organs.[1] They are also known as *phakomatosis* (from the Greek *phacos*, meaning lens, and *phaos*, meaning light, that is "tumor of the lenses" due to retinal affectation in some patients). The most common entities are tuberous sclerosis (Boyrneville disease), von Hippel-Lindau disease, Sturge-Weber syndrome (Sturge-Weber-Dimitri syndrome or encephalotrigeminal angiomatosis), and the focus of the present study: neurofibromatosis (NF).[1]

In this context, NF consists in three distinct entities with different genetic inheritance: type-1 NF (NF1) – classically known as von Recklinghausen disease or peripheral NF; type-2 NF (NF 2) – formerly known as central NF, characterized by the presence of vestibular schwannomas; and schwannomatosis (SCH) – a rare entity with multiple schwannommas but without vestibular schwannomas.[2] The main characteristic of all NFs is the high predisposition to the growth of multiple tumors in the entire body.

In the current study, we present a comprehensive narrative review, with illustrative cases of the main manifestations of NF1, focusing on the perspective of the spine surgeon.

Materials and Methods

An electronic search on the Pubmed database was performed on October 8th, 2021 using the following keywords: *neurofibromatosis* + *spine* + *surgery*. The author evaluated all abstracts and grouped them with the aim of discussing the management and characteristics of spinal diseases in the context of NF1.

Clinical cases from the database of the authors' institution were presented to illustrate the technical challenges and strategies that may be used to treat these patients (approval form the institutional review board was obtained under number 17337313.7.0000.5404). A total of 481 articles were screened, and cross-referenced articles were used when necessary. Articles were grouped according to the following subjects: diagnosis, skeletal complications, spinal deformity, and spinal tumors. For all of them, a detailed discussion on pearls for practice was presented.

Results

Diagnosis of NF1

The inheritance pattern of NF is autosomal dominant in about 50% of the cases, and sporadic (*de novo* mutation) in the remaining cases – due to a mutation in the long arm of chromosome 17 (*ras protein*). There is no gender predilection.

The diagnosis of the multisystem disease syndrome of NF1 is characterized by at least two out of seven criteria in the absence of an alternate diagnosis (►**Table 1**).[3–6]

Cutaneous findings are much more common in NF1 than in NF2, but the latter has a higher incidence of CNS tumors, even though patients with NF1 may have optic nerve

Table 1 Diagnostic criteria for type-1 neurofibromatosis (NF1) and their estimated prevalence

Diagnostic criteria*	Estimated prevalence
Six or more café-au-lait spots or hyperpigmented macules (> 5 mm in prepubertal patients or > 15 mm in postpubertal patients)	95%
> 2 freckles (axillary or inguinal)	87%
≥ 2 typical neurofibromas or one plexiform neurofibroma	40–60% and 35% respectively
Optic nerve glioma	6%
≥ 2 iris hamartoma (also known as Lisch nodules)	78%
Sphenoid dysplasia or typical long-bone abnormalities	5%
First-degree relative with NF1 (parent, sibling, or offspring defined by the aforementioned criteria)	50%

Note: *The diagnosis requires the fulfillment of at least two of the diagnostic criteria.

gliomas, spinal cord tumors, and vascular abnormalities in the CNS. Life expectancy is shorter for patients with NF1 (about 8 years lower than that of the general population), especially due to malignant transformation of neurofibromas (NFBs) and plexiform NFBs into malignant peripheral nerve sheath tumors (MPNSTs).[7]

The phenotypical expression of NF1 patients varies greatly, and its natural evolution is unpredictable.[8] As a rule, the phenotypical presentation of the disease is more pronounced with aging, since many patients present more prominent cutaneous findings between the fourth and fifth decades of life. Despite that, by the age of 3 years, 99% of NF1 patients present café-au-lait spots.[8]

Skeletal Complications in NF1

Skeletal changes, as well as other phenotype characteristics, may vary from focal to generalized bone disorders.[9] Focal changes include spinal deformities, pseudoarthrosis of the tibia and forearm, chest-wall deformities etc. Generalized disorders are more common and may include severe bone malformations with dysplasia, osteoporosis, osteomalacia, shortness of stature and macrocephaly.[9]

Another commonly-found skeletal change are defects of the posterosuperior wall of the orbit (it is also a diagnosis criterion of NF1), intrathoracic meningocele, erosive defects of the bone from contiguous neurogenic tumors, anomalies of lumbar segmentation, spina bifida occulta, among others.[9]

Although NF1 is basically characterized by dysplasia of the neurectoderm, there is also mesoblastic dysplasia associated, which is responsible for the skeletal and soft-tissue changes.[9] These mesoblastic defects explain why some patients may present with "elephantoid masses of soft tissue" anywhere in the body.[9] These masses may also contain a hemangiomatous component, which generally involves a lower limb unilaterally or the head and neck.

Spinal Deformities

More than 20% of NF1 patients have some degree of spinal deformity,[10–12] which may be dystrophic or not, and is classified according to the presence of at least three dystrophic components. The most common dystrophic spinal changes are presented in ►**Table 2**. They are associated with more pronounced progression of spinal deformities and a more unfavorable outcome (from a skeletal as well as from a neurological perspective).

Thoracic and Lumbar Scoliosis and Kyphoscoliosis

The most common spinal deformity found in patients with NF1 is scoliosis. The reasons for this high prevalence may be mesodermal dysplasia, osteomalacia, bone erosion, and endocrine disturbances. Considering a general outpatient scoliosis clinics, about 2% of the patients had NF1, but up to 20% of the NF1 patients had scoliosis.[10–12] Non-dystrophic patients have curvatures similar to those with idiopathic scoliosis, with less severe deformities than those with dystrophic curvatures.

As aforementioned, deformity in NF1 can be dystrophic or non-dystrophic, and fortunately the latter is more commonly found.[13] Three or more of the dystrophic features presented in ►**Table 2** categorize patients as having dystrophic deformities. The management of non-dystrophic deformity is basically the same as the one provided to non-NF1 patients, using similar algorithms for surgical indications, such as surgical treatment for curves of more than 40°. On the other hand, dystrophic deformities are associated with progressive deterioration, extremely severe deformities, and clinical dysfunction.[12,14] Some patients may initially present a

Table 2 Diagnostic criteria for dystrophic deformity*

Vertebral scalloping (characterized by a concavity in the posterior vertebral body wall observed in spinal images on lateral projection)
Widening of the vertebral canal and neural foramina
Spindling of the transverse process
Spinal deformities – scoliosis, kyphosis, or kyphoscoliosis
Severe rotation of the apical vertebra in spinal scoliosis
Dural ectasia
Defective pedicles (sometimes precluding spinal fixation using screws due to their small diameter)
Rib penciling

Note: *The diagnosis is established in the presence of three or more components.

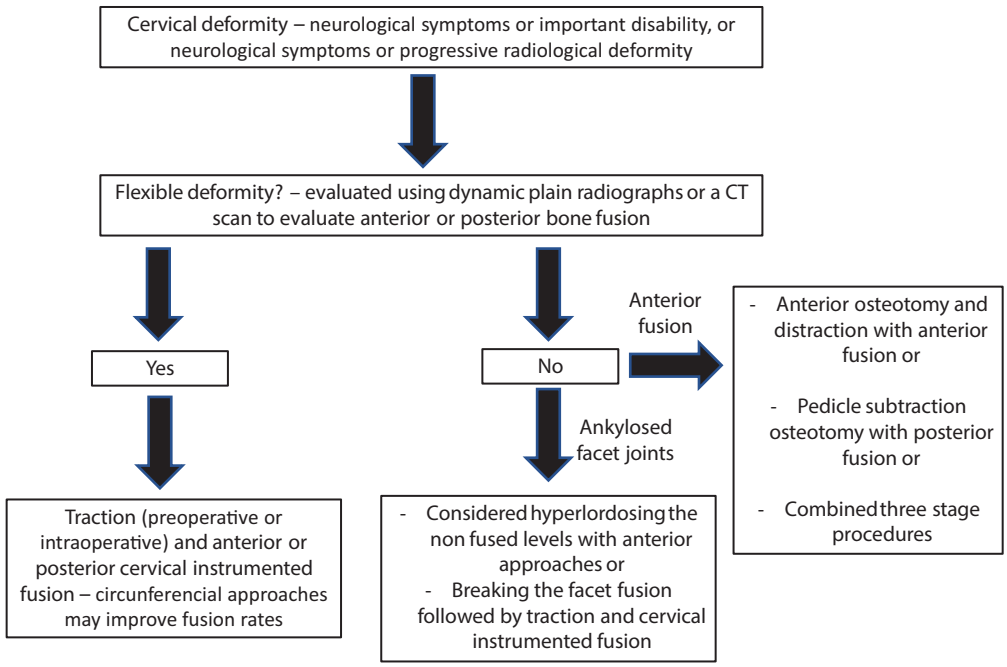

Fig. 1 Algorithm proposed to help in the management of cervical deformity. Adapted from Joaquim AF and Riew KD. Management of Cervical spine deformity after intradural tumor resection. Neurosurg Focus 2015;39(2):E13.

non-dystrophic deformity that can become dystrophic with aging.[15] Dystrophic deformities are associated with kyphosis, and they present a higher incidence of neurological deficits. In NF1, a magnetic resonance imaging (MRI) scan is recommended to all cases of spinal deformities since it is much more sensitive when it comes to detecting dystrophic changes. Some authors[16,17] have suggested that dystrophic curvatures should be surgically treated even if they present 20° to 40° due to their unfavorable and rapid evolution.

Challenges in dystrophic patients include poor bone quality, abnormal spinal anatomy, high severity of deformities, as well as difficulty in achieving fusion. Additionally, postlaminectomy deformities are more prominent in NF1 patients, especially those with dystrophic changes.

The most dramatic situation in NF1 is vertebral dislocation in highly-dystrophic kyphoscoliosis. This is a rare situation that may lead to neurological paraplegia and require complex procedures. In the spinal literature, some authors[18] have proposed the use of a halo-pelvic traction (HPT) apparatus – an external fixation system that provides a gradual correction (between one and two months) before the definitive surgical management – which is normally used between four and eight weeks before surgery. Halo-gravity traction (HGT) has also been proposed to improve curves preoperatively in cases of severe deformities, such as those with great evidence of the kyphotic element over the scoliotic curve with an acute angulation.[9] The rate of preoperative correction of the curve may be of about 40% with the preoperative use of HTP or HGT, decreasing the morbidity of the procedures and the need for more extensive osteotomies.

Cervical Kyphosis

Severe kyphosis is the most common cause of neurological deficits in NF1–in general, it is characterized by an acute anteroposterior angulation and deformed vertebral bodies that may be confused with congenital deformities. Cervical kyphosis may also be accompanied by a large neck NFB, which may increase the difficulty to treat these patients, as well as the morbidity of any eventual procedure.

Generally, some patients may need anteroposterior approaches for dystrophic cervical kyphosis, with higher potential for correction, even though only anterior or only posterior approaches may also be used.[19] Our algorithm to treat cervical kyphosis is presented in ►**Figure 1**[20] and an illustrative case is presented in ►**Figure 2**.

Most of the authors,[20] including us, have proposed that moderate correction is a reasonable and safer strategy in severe dystrophic cervical kyphosis.

The strategies described to treat severe cervical kyphosis include osteotomies followed by traction and definitive surgery; HGT is commonly reported[21] as a useful tool for severe cervical kyphosis or even severe kyphoscoliosis that should be employed preoperatively for four to six weeks to improve spinal alignment, decreasing the morbidity of the procedures.

Spinal tumors

Neurofibromas

The most common tumor found in NF1 patients are NFBs, followed by plexiform NFBs, MPNSTs, and glial tumors.[22] Contrary to NF2, the tumors are less frequently found in the intradural spinal compartment in NF1 (less than 10% of the cases), with most of them located laterally to the neuroforamina.[23]

The symptoms may include neuropathic pain, paresthesia, and even motor and sensory deficits due to spinal cord compression. Surgery is also considered for those with a

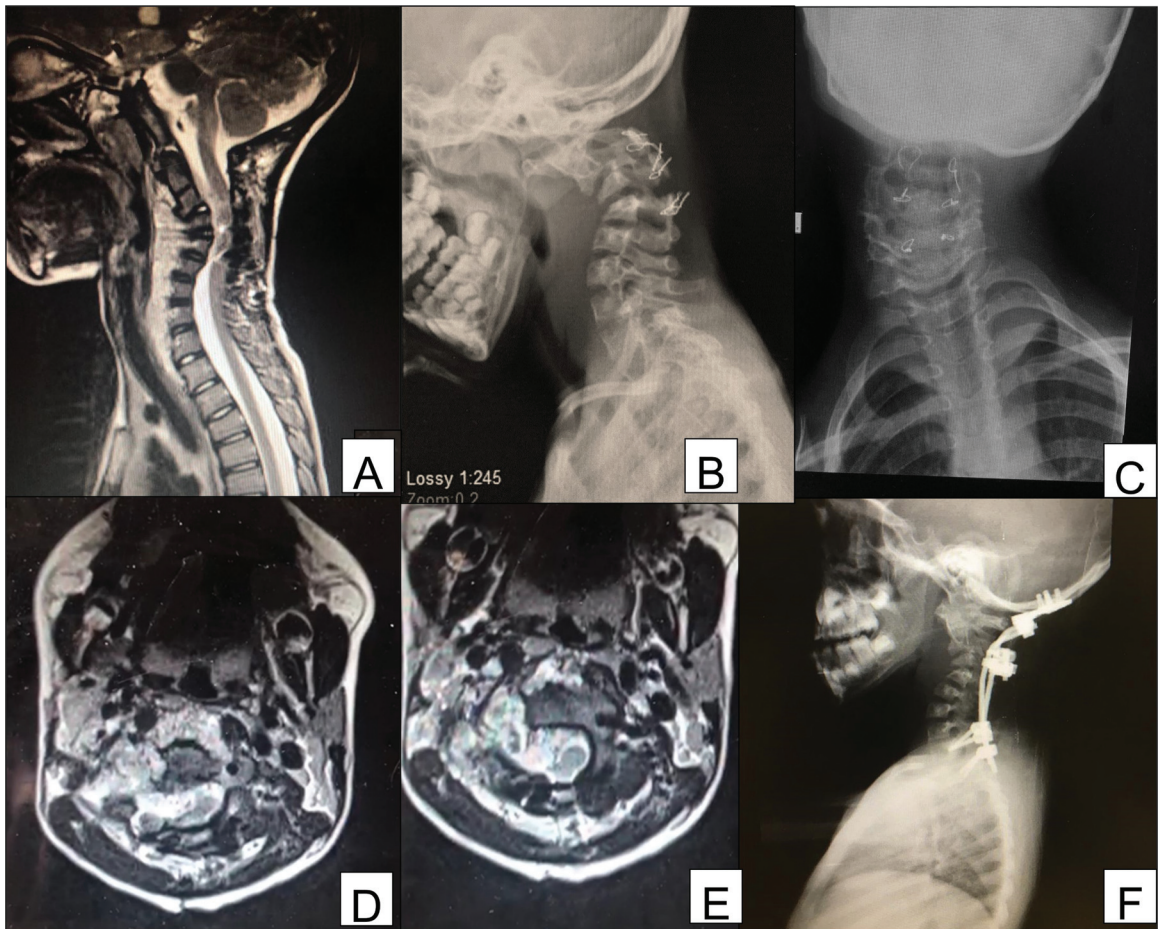

Fig. 2 A 6 year-old boy who underwent a previous C2-3-4 laminoplasty for resection of an intradural neurofibroma developed postoperative cervical kyphosis, with important pain and difficulty in swallowing, as shown in (**A**) the sagittal cervical magnetic resonance imaging (MRI) scan in T2-weighted sequence, and (**B**) in lateral and (**C**) anteroposterior plain cervical radiographs. Since the patient also had a giant anterior cervical neurofibroma, as shown in (**A**) and in (**D, E**) – axial T2-weighted sequence cervical MRI, the option of an anterior cervical surgery with tumor resection was refused by his parents due to the need of postoperative tracheostomy. We opted for preoperative traction using progressive adjustments of a halo vest for six weeks, followed by posterior occipito-cervico-thoracic fusion, because the lateral masses were too small and dysplastic for screw fixation. The patient presented persistent residual segmental kyphosis but with a good and acceptable head position after surgery, with significant improvement in symptoms.

suspicion of malignant transformation. Large dumbbell tumors, especially in the cervical spine, may require combined cervical approaches. The need for a combined or an isolated cervical approach depends on the extension of the NFB anteriorly or posteriorly, as well as the involvement of the vertebral artery. ►**Figure 3** presents an illustrative NFB found in a routine plain thoracic radiograph.

Taleb et al.[24] reported the results of 22 cases of cervical spine NFB operated on at their institution. The mean age at presentation was of 42.5 years, and most of the patients had progressive myelopathy. In total, 11 (50%) underwent complete tumor removal, and 10 were submitted to spinal instrumented fusion during the first procedure, 6 of them requiring an additional procedure. Overall, 8 out of the 12 patients who did not undergo instrumented fusion at the first surgery required a second procedure, 5 of which included instrumented fusion. Finally, four patients required a third procedure and instrumented fusion. Most of the patients required instrumented fusion at some point of the follow-up. One patient died in this series. The lesson learned is that decompressive procedures in the cervical spine in NF1 patients will ultimately cause some degree of deformity, even in adult patients.

Sometimes, NFBs are found bilaterally in two nerve roots at the same spinal level, resulting in significant cord compression. These typical lesions are known as "kissing neurofibromas" and symptomatic tumors (generally with progressive myelopathy in the cervical spine) are surgically treated to relieve cord compression (►**Figure 4**).[25] Cervical spine "kissing" tumors are more prone to require surgical treatment than lumbar tumors due to the presence of the spinal cord.[25]

Plexiform NFBs are present in about 30% to 50% of NF1 patients, and they may degenerate in about 10% of the cases to malignant transformation.[26] They are diffuse tumors that involve multiple nerve branches and trunks, potentially reaching very large dimensions. Radiologically, they generally present a hypointense signal in T1-weighted sequences, and hyperintense signal in T2-weighted sequences and short-tau inversion recovery (STIR), with central areas of

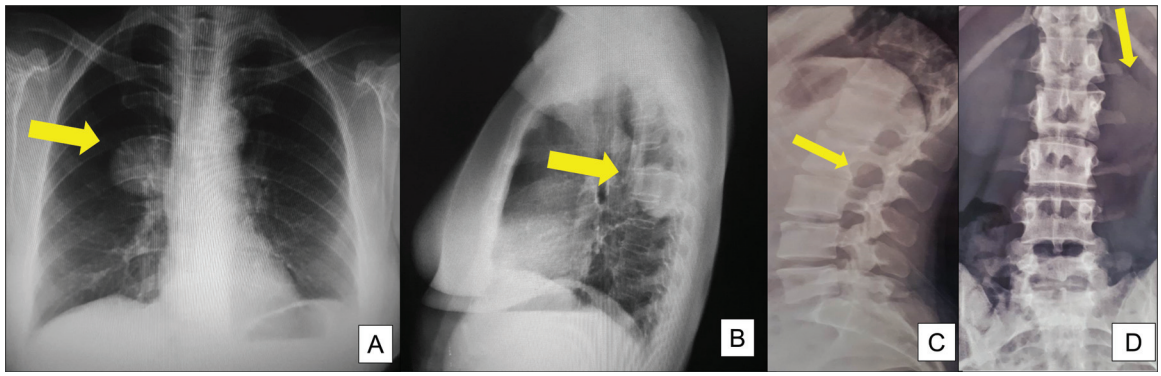

Fig. 3 Anteroposterior (**A**) and lateral (**B**) plain thoracic radiographs of an NF1 patient, showing a thoracic mass (yellow arrows). Another illustrative case – Lateral (C) and anteroposterior (D) plain lumbar radiographs of a patient complaining of lumbar pain, showing an enlargement of the neural foramen and pedicle remodeling (yellow arrow – C) as well as amass between the transverses process of the upper lumbar spine (yellow arrow – D).

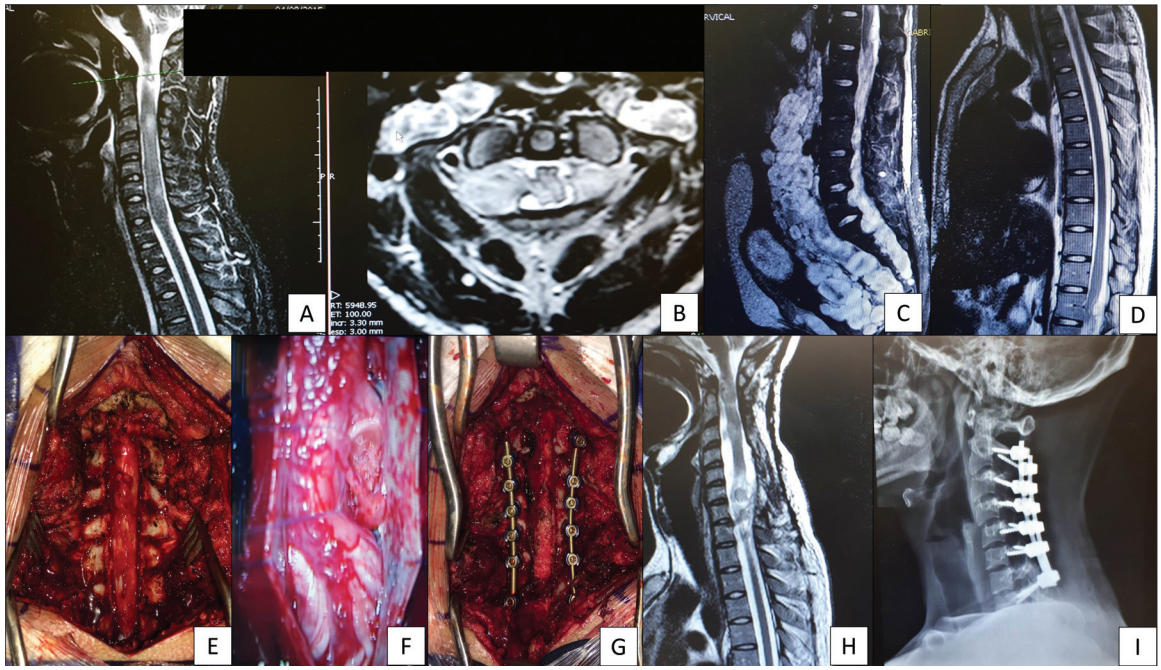

Fig. 4 Sagittal (**A**) and axial (**B**) cervical T2-weighted sequence MRI scans of an 18-year-old patient with multiple kissing neurofibromas and severe tetraparesis. He underwent a C2–C7 laminectomy with duroplasty for enlargement of the spinal canal with microsurgical partial resection of the multiple neurofibromas guided by neurophysiological monitoring (F). C2–T1 posterior instrumented fusion was performed to avoid postlaminectomy deformity. Postoperative sagittal T2-weighted sequence MRI showing good spinal cord decompression (**H**); final plain cervical lateral radiograph (**I**). The neurofibroma at T12 was also submitted to surgery, and the patient had great improvement in his neurological deficits.

low signal. The clinical symptoms may include mass effect, pain, bone changes/deformity, intratumoral bleeding, neural compression symptoms, and malignant transformation.

Surgery for non-malignant NFB is generally indicated for symptomatic lesions with progressive deficits, since it is not feasible to remove all asymptomatic tumors and most of the patients only undergo partial tumor removal due to the neurological morbidity of an aggressive surgery.[22]

Anecdotal case reports have suggested that the mitogen-activated protein kinase (MEK) inhibitor may cause shrinkage of plexiform NFBs. Vaassen et al.[27] reported the case of an 11 year-old NF1 patient who had a reduction of about 22% of a large plexiform NFB after 6 months of therapy. Further studies are necessary to evaluate the impact of the use of MEK inhibitor in tumor control.

In the case of suspicious of histological malignant transformation, such as large tumors or rapid tumor growth with or without persistent pain, fluorodeoxyglucose (FDG)-positron emission tomography (PET) is recommended in conjunction with MRI to perform an early diagnosis.[28] Generally, MPNSTs present high fluorodeoxyglucose (FDG) uptake and large dimensions (those larger than 6 cm are very suspicious).[29] Commonly found in NF1 patients in the second and third decades of life, MPNSTs are very aggressive lesions. They are the most common malignant tumor in NF1, with an impact on overall survival. The best treatment modality is

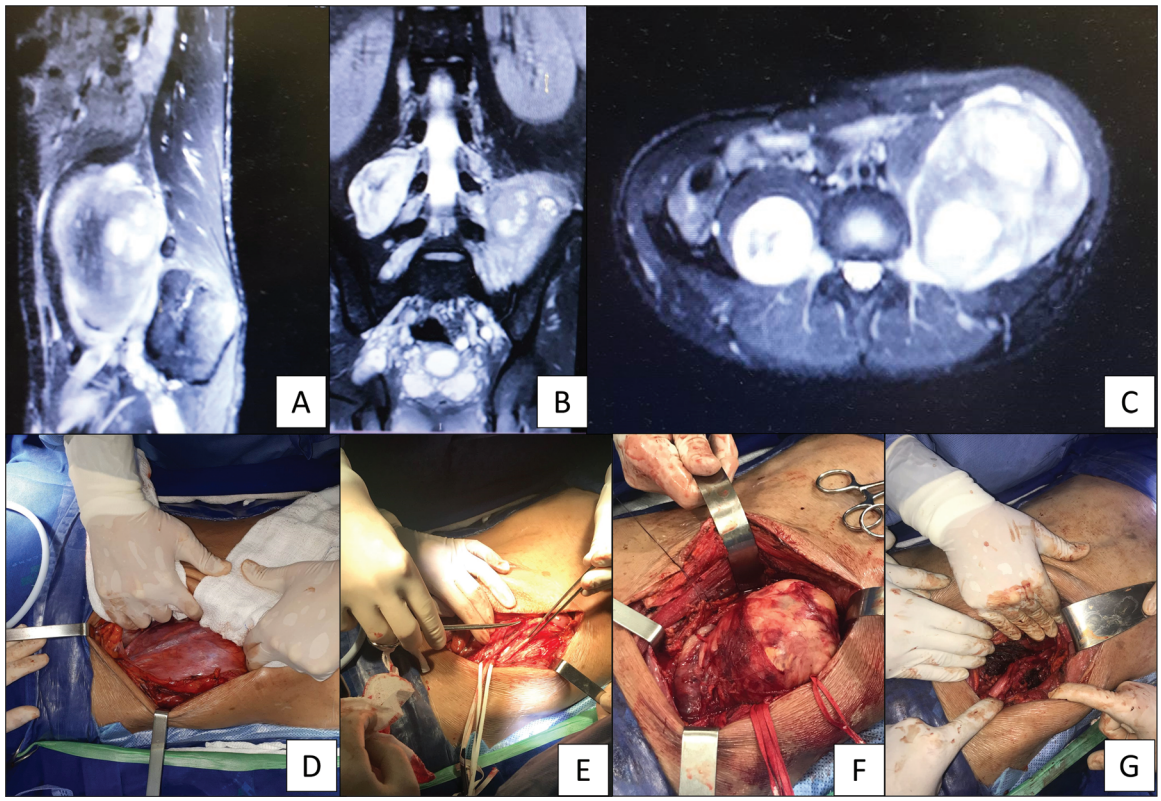

Fig. 5 An 18-year-old NF1 patient who complained of an abdominal mass and constipation. He had a giant left retroperitoneal neurofibroma, as shown in the sagittal (**A**), coronal (**B**), and axial (**C**) abdominal CT scans. A left retroperitoneal approach was performed (**D**), and we identified and isolated the multiple nerves of the lumbar sacral plexus (**E**) through en bloc resection of the mass (**F**). Total resection of the malignant peripheral nerve sheath tumor was achieved (**G**).

aggressive surgical resection. Incomplete resection may be treated with adjuvant chemotherapy with doxorubicin and ifosfamide. Radiotherapy is controversial, and its role is still under debate. ►**Figure 5** presents an illustrative case of MPNST that was surgically treated.

Finally, as aforementioned, postoperative instability is much more common in NF1 patients submitted to spinal laminectomy for intracanal tumor removal due to tumor-related changes, bone reabsorption, bone dystrophia, and osteoporosis. Therefore, closer radiological and clinical follow-ups for the early diagnosis of deformities recommended in cases in which it was not clear at the time of the surgery for tumor resection if instrumented fusion would be beneficial. Dural ectasia and lateral meningoceles, the soft components of NF1, may lead to weakness of the spine and favor deformities.[30]

Intramedullary Tumors

Intramedullary tumors are less common in NF1 than in NF2 patients.

The most common intracranial tumors in NF1 are pilocytic astrocytomas that preferentially involve the optic nerves and chiasm. The same is true for intramedullary spinal cord tumors (IMSCTs). Kushel' et al.[31] have reported that, in a large series of 541 patients with IMSCT, 7 patients had NF1–5 of whom with pilocytic astrocytoma, 1 with an anaplastic astrocytoma (the only adult patient with NF1, aged 51 years), and 1 with a thoracic ependymoma –, mostly children and adolescents. Only for the purpose of comparison, considering the 15 patients with NF2, 12 of them had ependymoma, 2 had pilocytic astrocytoma, and 1 presented a fibrillary astrocytoma. Their findings[31] suggest a strong link between astrocytoma and NF1 in children and adolescents, and ependymomas and NF2.

The generally accepted indications for surgery are symptomatic or asymptomatic tumors with progressive radiological findings.

Though rare, other histologies have been reported in NF1, such as gangliogliomas, primitive neuroectodermal tumors (PNETs), anaplastic astrocytomas, and even neurinomas have been reported anecdotally.[32–34]

The surgical treatment for IMSCT consists in resection of as much tumor as possible guided by neurophysiological monitoring, to avoid further neurological deficits. Ependymomas and some pilocytic astrocytomas may be totally resected in some cases of focal and circumscribed tumors. For malignant astrocytomas, adjuvant chemotherapy and radiotherapy may also be considered, despite a very unfavorable outcome.

Chalenges in Spinal Surgery in NF1

The very thin laminae of some patients, due to tumor erosion or dural ectasia, may preclude the use of hooks, wires, and screws. Therefore, a careful examination of bone anatomy through computed tomography (CT) scans is advisable before the development of a surgical plan.

Cerebrospinal fluid leak due to the very thin laminae is also a potential complication that may be decreased with diligent dissection and external lumbar drains when necessary.

Extensive bleeding from venous lakes and from blood vessels in the cancellous bone requires the use of hemostatic agents and proper anesthetic support.

Patients with NF1 frequently need to consult with a spinal surgeon and close clinical and radiological follow-ups. Understanding the nuances of the diseases, as well as the variability in presentations, is of paramount importance to properly manage these patients and decrease the suffering caused by this morbid syndrome.

Conflict of Interests

The author has no conflict of interests to declare.

References

1 Klar N, Cohen B, Lin DDM. Neurocutaneous syndromes. Handb Clin Neurol 2016;135:565–589
2 Plotkin SR, Wick A. Neurofibromatosis and Schwannomatosis. Semin Neurol 2018;38(01):73–85
3 National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987. Neurofibromatosis 1988;1(03):172–178
4 Trovó-Marqui AB, Goloni-Bertollo EM, Valério NI, et al. High frequencies of plexiform neurofibromas, mental retardation, learning difficulties, and scoliosis in Brazilian patients with neurofibromatosis type 1. Braz J Med Biol Res 2005;38(09): 1441–1447
5 Darrigo LG Jr, Geller M, Bonalumi Filho A, Azulay DR. Prevalence of plexiform neurofibroma in children and adolescents with type I neurofibromatosis. J Pediatr (Rio J) 2007;83(06):571–573
6 Souza JFd, Toledo LLd, Ferreira MCM, et al. Neurofibromatosis type 1: more frequent and severe then usually thought. Rev. Assoc. Med. Bras (1992); 55(4): 394–399, 2009. graf, tab Artigo em Português | LILACS | ID: lil-525042
7 Wilding A, Ingham SL, Lalloo F, et al. Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet 2012;49(04):264–269
8 Rodrigues LO, Batista PB, Goloni-Bertollo EM, et al. Neurofibromatoses: part 1 - diagnosis and differential diagnosis. Arq Neuropsiquiatr 2014;72(03):241–250
9 Hunt JC, Pugh DG. Skeletal lesions in neurofibromatosis. Radiology 1961;76(01):1–20
10 Khong P-L, Goh WHS, Wong VCN, Fung CW, Ooi GC. MR imaging of spinal tumors in children with neurofibromatosis 1. AJR Am J Roentgenol 2003;180(02):413–417
11 Hsu LC, Lee PC, Leong JC. Dystrophic spinal deformities in neurofibromatosis. Treatment by anterior and posterior fusion. J Bone Joint Surg Br 1984;66(04):495–499
12 Sirois JL III, Drennan JC. Dystrophic spinal deformity in neurofibromatosis. J Pediatr Orthop 1990;10(04):522–526
13 Ramachandran M, Tsirikos AI, Lee J, Saifuddin A. Whole-spine magnetic resonance imaging in patients with neurofibromatosis type 1 and spinal deformity. J Spinal Disord Tech 2004;17(06):483–491
14 Crawford AH. Pitfalls of spinal deformities associated with neurofibromatosis in children. Clin Orthop Relat Res 1989:29–42 25.
15 Durrani AA, Crawford AH, Chouhdry SN, Saifuddin A, Morley TR. Modulation of spinal deformities in patients with neurofibromatosis type 1. Spine 2000;25(01):69–75
16 Li M, Fang X, Li Y, Ni J, Gu S, Zhu X. Successful use of posterior instrumented spinal fusion alone for scoliosis in 19 patients with neurofibromatosis type-1 followed up for at least 25 months. Arch Orthop Trauma Surg 2009;129(07):915–921
17 Tauchi R, Kawakami N, Castro MA, et al. Long-term Surgical Outcomes After Early Definitive Spinal Fusion for Early-onset Scoliosis With Neurofibromatosis Type 1 at Mean Follow-up of 14 Years. J Pediatr Orthop 2020;40(01):42–47
18 Wang Y, Li C, Liu L, Qi L. Halo-pelvic traction for thoracic spine dislocation in neurofibromatosis type 1: a case series. Arch Orthop Trauma Surg 2022;142(04):571–577
19 Lin T, Shao W, Zhang K, Gao R, Zhou X. Comparison of Outcomes in 3 Surgical Approaches for Dystrophic Cervical Kyphosis in Patients with Neurofibromatosis 1. World Neurosurg 2018;111: e62–e71
20 Joaquim AF, Riew KD. Management of Cervical spine deformity after intradural tumor resection. Neurosurg Focus 2015;39(02): E13
21 Kurucan E, Bernstein DN, Thirukumaran C, et al. National Trends in Spinal Fusion Surgery for Neurofibromatosis. Spine Deform 2018;6(06):712–718
22 Shimizu T, Lenke LG, Cerpa M, Lehman RA Jr, Pongmanee S, Sielatycki JA. Preoperative halo-gravity traction for treatment of severe adult kyphosis and scoliosis. Spine Deform 2020;8(01): 85–95
23 Shofty B, Barzilai O, Khashan M, Lidar Z, Constantini S. Spinal manifestations of Neurofibromatosis type 1. Childs Nerv Syst 2020;36(10):2401–2408
24 Thakkar SD, Feigen U, Mautner VF. Spinal tumours in neurofibromatosis type 1: an MRI study of frequency, multiplicity and variety. Neuroradiology 1999;41(09):625–629
25 Taleb FS, Guha A, Arnold PM, Fehlings MG, Massicotte EM. Surgical management of cervical spine manifestations of neurofibromatosis Type 1: long-term clinical and radiological follow-up in 22 cases. J Neurosurg Spine 2011;14(03):356–366
26 Shofty B, Mauda-Havakuk M, Ben-Sira L, et al. Surgical Management of "Kissing" Spinal Plexiform Neurofibromas in Neurofibromatosis Type 1 Patients. World Neurosurg 2020;134: e1143–e1147
27 Goertz O, Langer S, Uthoff D, et al. Diagnosis, treatment and survival of 65 patients with malignant peripheral nerve sheath tumors. Anticancer Res 2014;34(02):777–783
28 Vaassen P, Dürr N, Röhrig A, Willing R, Rosenbaum T. Trametinib Induces Neurofibroma Shrinkage and Enables Surgery. Neuropediatrics 2019;50(05):300–303
29 Reinert CP, Schuhmann MU, Bender B, et al. Comprehensive anatomical and functional imaging in patients with type I neurofibromatosis using simultaneous FDG-PET/MRI. Eur J Nucl Med Mol Imaging 2019;46(03):776–787
30 Marjanska A, Galazka P, Wysocki M, Styczynski J. New frontiers in therapy of peripheral nerve sheath tumors in patients with neurofibromatosis type 1: latest evidence and clinical implications. Anticancer Res 2020;40(04):1817–1831
31 Tsirikos AI, Saifuddin A, Noordeen MH. Spinal deformity in neurofibromatosis type-1: diagnosis and treatment. Eur Spine J 2005;14(05):427–439
32 Kushel' YV, Belova YD, Tekoev AR. [Intramedullary spinal cord tumors and neurofibromatosis]. Vopr Neirokhir 2017;81(01):70–73
33 Hayashi Y, Nakada M, Mohri M, Murakami H, Kawahara N, Hamada J. Ganglioglioma of the thoracolumbar spinal cord in a patient with neurofibromatosis type 1: a case report and literature review. Pediatr Neurosurg 2011;47(03):210–213
34 Mulholland CB, Barkhoudarian G, Cornford ME, McBride DQ. Intraspinal primitive neuroectodermal tumor in a man with neurofibromatosis type 1: Case report and review of the literature. Surg Neurol Int 2011;2:155
35 Nicoletti GF, Passanisi M, Castana L, Albanese V. Intramedullary spinal neurinoma: case report and review of 46 cases. J Neurosurg Sci 1994;38(03):187–191

What a Neurosurgeon Should Know About the Endolymphatic Sac: Part 3 – Ménière Disease

O que um Neurocirurgião Deve Saber Sobre o Saco Endolinfático: Parte 3 – Doença de Ménière

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Abstract

Objective To elucidate all the aspects that neurosurgeons should know about the Ménière disease (MD).

Methods Review of guidelines, books, and studies from 1933 to 2021, from basic to translational research, using human and animal endolymphatic sac (ES) tissue or cells, as well as reviews, case reports, and papers about surgical experience. This article is divided into three parts. In this last part, we review the MD.

Results The MD is one of the most common pathologies in the ES. It was first described by Prosper Ménière in 1861 with its clinical triad: dizziness, tinnitus, and hearing loss. A lot of theories relating ES to the MD have been proposed. Some of them postulate that it is caused by a narrowing and shortening in the endolymphatic duct, and others relate it to severe inflammation on the ES. Mostly due to the lack of understanding of this pathology, the diagnosis is mainly clinical, despite histopathology being helpful to confirm the diagnosis. The treatment of the MD can be done in 3 different ways: pharmacological, nonpharmacological, and surgical.

Conclusion The MD is one of the most common pathologies in the inner ear and has been largely studied over the years. The latest diagnosis guidelines must help in the classification and give better basis for diagnosis and treatment, which, despite not

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being curative yet, has improved over the years. Pharmacological treatment based on the possible etiologies, allied with proper diet and routine exercise, is showing promising results.

Resumo

Objetivo Elucidar todos os aspectos que neurocirurgiões devem saber sobre a doença de Ménière (DM).

Métodos Revisão das diretrizes, livros e estudos de 1933 até 2021, de pesquisa básica até translacional, usando tecidos ou células do saco endolinfático (SE) humanas e animais, além de revisões, relatos de caso e artigos sobre experiencia cirúrgica. Este artigo é dividido em três partes. Nesta última nós revisamos a DM.

Resultados A DM é uma das patologias mais comuns do SE. Ela foi inicialmente descrita por Prosper Ménière em 1861 com a tríade clínica: tontura, zumbido e diminuição da audição. Muitas teorias têm relacionado o SE com a DM. Algumas delas postulam que esta é causada por uma diminuição e estreitamento do ducto endolinfático e outras a relacionam com uma inflamação grave do SE. Principalmente devido à falta de entendimento sobre a patologia, o diagnóstico é primariamente clínico, apesar da Histopatologia ajudar na confirmação diagnóstica. O tratamento da DM pode ser feito de três diferentes formas: farmacológico, não farmacológico e cirúrgico.

Conclusão A DM é um dos distúrbios mais comuns da orelha interna e tem sido muito estudada nos últimos anos. As diretrizes mais recentes devem ajudar na classificação e fornecer mais bases para o diagnóstico e tratamento, que, apesar de ainda não ser curativo, teve grandes avanços ao longo dos anos. O tratamento farmacológico baseado nas teorias etiológicas, aliado com dieta apropriada e exercícios físicos rotineiros, tem mostrado excelentes resultados.

Palavras-chave
- saco endolinfático
- doença de Ménière
- neurocirurgia

Introduction

The endolymphatic sac (ES) is a structure situated in the inner ear, together with the cochlea and the semicircular canals, or vestibular system.[1] The ES may be responsible for homeostatic regulation of the inner ear, endolymphatic fluid volume, immune response, elimination of inner ear cellular debris and floating otoconia, membranous labyrinth pressure, acid/basic transport, and the secretion of substances.[1–11]

Despite being only 3 mm long in diameter, the ES does not have a very variable location inside the inner ear.[8] Almost every alteration in this structure can cause a massive problem to the hearing, including its loss. The Ménière disease (MD) is one of the most common pathologies of the ES,[12] and it was first described by Prosper Ménière in 1861, with its clinical triad: dizziness, tinnitus, and hearing deafness, with or without aural fullness. Over the years, a lot has changed regarding the definition of this disease but some aspects, like the etiology, are still in debate.[13]

The MD can be treated surgically. Two of the possible procedures are ES decompression and vestibular neurectomy. Pharmacological and nonpharmacological treatments can also help.[12,14]

In this review, our aim is to elucidate all the aspects that neurosurgeons should know about MD.

Methodology

This article is divided into three parts. In the third part we review the MD's basic aspects, clinical diagnosis and treatment. We focused on evidence of guidelines, books, and PubMed (from 1933 to 2021) basic and translational research, using human and animal ES tissue or cells, previous reviews about the subject, case reports, and papers about surgical experience. The terms used individually and combined were: *Endolymphatic sac*; *Ménière disease*; *Neurosurgery*. Literature inclusion criteria were: English and Portuguese language only; individual case studies and long-term follow-up studies were included, and duplicate studies were excluded.

First, we briefly approached the basic aspects of MD and its relation to the ES, followed by a review of the clinical diagnosis and treatment. This study may provide a basis to guide neurosurgeons in the evaluation and treatment of this disease.

Results

Basic Aspects and Relation to the ES

The MD was first described by Prosper Ménière in 1861 with its clinical triad: dizziness, tinnitus, and hearing deafness, with or without aural fullness.[13] However, although some of

these original aspects are still present in guidelines, a lot more has been discovered about this disease.

The MD commonly affects adults from 20 to 50 years[13] and is more likely to occur in women.[15] Both ears are affected with the same frequency. Despite the large number of recent studies about the MD, the epidemiology is still unclear, bearing in mind how difficult it is to make an early diagnosis.[13] Although challenging to measure, Alexander and Harris[15] estimate that the prevalence of MS in the United States is 190 per 100,000 habitants.

Part of the trouble in making an early diagnosis of MD lies in its unclear etiology.[13] Studies have raised many theories on its possible causes, but none of them were confirmed. Some of the theories are related to the ES, such as the possibility of a narrowing and shortening in the endolymphatic duct that could hamper the reabsorption of endolymph in the ES, since a smaller duct would allow less endolymph to pass through the duct. Thus, the retained endolymph would elevate the pressure in the endolymphatic space.[13] Another possibility is a reduction of the ES itself, again hampering the reabsorption properties of the ES since the contact surface is smaller.[13] In agreement with that, an experimental obliteration of the ES caused MD symptoms.[16]

It's also possible that due to the immunological properties of the ES,[2,5,6] the occurrence of severe inflammation on the ES contributes to tissue fibrosis, further damaging the structure and its function, and generating MD.[13] Another theory, described by Cahali et al.,[13] is related to the stria vascularis, and claims that patients with MD have a significant decrease in the number of vessels, with its transversal section also being smaller. Thus, the vascular deficiency of the stria vascularis represents a possible etiology, mostly because of its importance for the endocochlear potential and endolymph secretion.[13]

There are other explanations for the etiology of MD that are not related to the ES. Glycemic and insulin disorders have been described as possible causes since 90% of the patients with MD have alterations in the glucose and/or insulin levels. Besides that, diet and exercise can diminish the symptomatology of the patients.[13] Hypothyroidism and estrogen insufficiency are among other possible causes.[13]

With fewer observational studies, some authors defend the hypothesis of food allergies (meat, corn, wheat etc.) and stress causing the MD.[13]

Clinical Diagnosis

The diagnosis of the MD is mainly clinical. Cochlear and vestibular symptoms with aural fullness, in the absence of neurological symptoms, characterize the disease. The MD attacks typically last from minutes to hours, and 96% of the cases also present neurovegetative symptoms. Bilateral tinnitus and hyperacusis are also very common, and can persist during and after the crises, in some cases becoming chronic. Other symptoms are: unilateral loud noise intolerance and sound frequencies distortion.[13]

Despite diagnosis criteria being mainly clinical, some exams can be done to confirm the suspicion.[13] Magnetic resonance imaging (MRI),[16] pure tone audiometry, glycerol test,[17] otoacoustic transport, standard vestibular test, retrocochlear tests, and glycemic and insulin curves[13] can be very helpful. Nevertheless, none of those exams are pathognomonic.[13]

The histopathological exam is the only one that comes close to confirming the diagnosis. Paparella determined that the most important histopathology finding in the MD is the endolymphatic hydrops in the cochlea and saccule. Also, saccule membrane bulging is a common finding.[18]

Using all this information, in 2015, the Barany Society made a guideline for the diagnosis of MD (►**Fig. 1**) and created simple and easily applicable diagnosis criteria.[19]

Treatment

The MD has 3 different types of treatment: pharmacological, nonpharmacological, and surgical.[13] The pharmacological aim is to do a symptomatologic aid, since none of the drug trials were proven to contribute to the healing process. Some of the choices include: hydrochlorothiazide, which increases the potassium concentration in the endolymph, labyrinth depressors, which have anticholinergics, antiemetics, and sedatives. Corticosteroids and vasodilators can also be used, based on the etiology hypothesis of, respectively, fibrosis due to severe inflammation of the ES or stria vascularis ischemia.[13]

Concerning the nonpharmacological treatment, it's possible to interfere in the patient's quality of life with dietary recommendations and routine exercise. A very similar diet for diabetic patients can be used to treat MD, since the high glucose levels can be an etiological factor. Accordingly, a diet rich in potassium and with lower sodium levels may also help. Alcohol consumption and smoking must stop, as well as caffeine, of which can be consumed a maximum of 250 mg per day.[13]

Regarding surgical treatment, two procedures stand out: ES decompression and vestibular neurectomy.[14] The ES procedure for MD was described for the first time by Portmann[20] and it is still used to treat patients' impairment with refractory MD. Hearing impairment and vertigo are the symptoms that have the largest improvement: 19% and 81%, respectively.[14] The operation starts with a bone incision at the retroauricular sulcus level, followed by mastoid opening to expose the lateral sinus. The bony wall of the lateral sinus is separated from the adjacent dura mater (DM), which is then elevated to until it reaches the adherence with the bone. After the vestibular aqueduct and the wall of the fossa are on the same level, it is possible to open the ES. First, the endolymphatic fossa is exposed and pierced in 2 to 3 mm on the ES wall. Afterwards, the opening of the ES must be done in a very delicate way in the connecting point between the dura mater and the rear wall of the petrosal bone.[20]

In 1933, Dandy[21] made the vestibular neurectomy common, but because of the collateral effects and postoperative complications, the procedure was not widely done. In 1991, 58 years later, Silverstein and Rosenberg[22] modified the previous technique and proposed what they called the "combined retrosigmoid/retrolabyrinthine vestibular nerve section". This technique demonstrated an 85% cure rate, with

Definitive Meniere disease[•]	
A.	Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours
B.	Audiometrically documented low to medium frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during, or after one of the episodes of vertigo
C.	Fluctuating aural symptoms (hearing, tinnitus, and fullness) in the affected ear
D.	Not better accounted for by another vestibular diagnosis
Probable Meniere disease	
A.	Two or more episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours
B.	Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
C.	Not better accounted for by another vestibular diagnosis

[•]No serological or genetic marker is considered for the diagnosis of MD.

Fig. 1 Ménière disease classification. Adapted from Lopez-Escamez JA et al.[19]

a 7% chance of enhancing the vertigo. Regarding the hearing loss, Silverstein and Rosenberg identified that 20% of the patients had a change on their audiometry compared to before the surgery and 4% showed substantial hearing loss.[12]

The "combined retrosigmoid/retrolabyrinthine vestibular nerve section" makes a U-shape incision in the postauricular area. Then, a mastoidectomy is required to expose the posterior fossa and the lateral venous sinus. Following, a dural incision is made to reach the cerebellum. The next step is to open the cerebellopontine angle (CPA) arachnoid over the ninth cranial nerve, with the intention of releasing CPA liquid, and releasing the pressure. With the decompression, the cerebellum disconnects itself from the temporal bone allowing for CPA exposure without damaging the cerebellar retraction. At this point, the facial nerve must be identified to prevent damaging it, and the eighth cranial nerve must be examined. After all precautions are taken, the vestibular nerve separation is performed in a cleavage plane between the cochlear and vestibular fibers. If the identification of the cleavage plane fails, the dura mater is reflected off the temporal bone, and the opening of the internal auditory canal is performed using a diamond burr, to enable the division of the superior vestibular and posterior ampullary nerves. To close, the mastoid air cells are sealed with bone wax and the dura with watertight fashion suture. The bony defect is corrected with adipose tissue to present fistulas.[22]

Conclusion

The MD is one of the most common pathologies of the inner ear and has been largely studied over the years. Its diagnosis is mainly clinical, which allows a bigger autonomy for medical professionals, but also demands a lot of experience. The latest guidelines must help in the classification of the disease and offer a better basis for diagnosis and treatment options.

The treatment, despite not being curative yet, has improved a lot recently. The pharmacological treatment based on the possible etiologies, allied with proper diet and exercise, is showing promising results. Surgical treatments, especially ES decompression, are procedures that must be taken into consideration for patients who don't respond well to noninvasive therapeutics, and for those who fill the necessary criteria. Knowing this, we highlight the importance of a well-trained doctor to identify and offer the best treatment possible. This study may provide a basis to acquire these skills.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Kim SH, Nam GS, Choi JY. Pathophysiologic Findings in the Human Endolymphatic Sac in Endolymphatic Hydrops: Functional and Molecular Evidence. Ann Otol Rhinol Laryngol 2019;128 (6_suppl):76S–83S
2 Altermatt HJ, Gebbers JO, Müller C, Arnold W, Laissue JA. Human endolymphatic sac: evidence for a role in inner ear immune defence. ORL J Otorhinolaryngol Relat Spec 1990;52(03):143–148
3 Arnold W, Altermatt HJ, Arnold R, Gebbers JO, Laissue J. Somatostatin (somatostatinlike) immunoreactive cells in the human inner ear. Arch Otolaryngol Head Neck Surg 1986;112(09): 934–937

4 Arnold W, Altermatt HJ, Gebbers J-O, Laissue J. Secretory immunoglobulin A in the human endolymphatic sac. An immunohistochemical study. ORL J Otorhinolaryngol Relat Spec 1984;46(06):286–288
5 Harris JP. Immunology of the inner ear: evidence of local antibody production. Ann Otol Rhinol Laryngol 1984;93(2 Pt 1):157–162
6 Harris JP. Immunology of the inner ear: response of the inner ear to antigen challenge. Otolaryngol Head Neck Surg 1983;91(01):18–32
7 Kawauchi H, Ichimiya I, Kaneda N, Mogi G. Distribution of immunocompetent cells in the endolymphatic sac. Ann Otol Rhinol Laryngol Suppl 1992;157(01):39–47
8 Lundquist PG. Aspects on endolymphatic sac morphology and function. Arch Otorhinolaryngol 1976;212(04):231–240
9 Mori N, Miyashita T, Inamoto R, et al. Ion transport its regulation in the endolymphatic sac: suggestions for clinical aspects of Meniere's disease. Eur Arch Otorhinolaryngol 2017;274(04):1813–1820
10 Tomiyama S, Harris JP. The role of the endolymphatic sac in inner ear immunity. Acta Otolaryngol 1987 May-Jun;103(5–6):182–188. Doi: 10.3109/00016488709107782. PMID: 21449640
11 Tomiyama S, Harris JP. The role of the endolymphatic sac in inner car immunology. Acta Otolaryngol 1987;103(01):182–188
12 Sajjadi H, Paparella MM. Meniere's disease. Lancet 2008 Aug 2;372(9636):406–414. Doi: 10.1016/S0140-6736(08)61161-7. PMID: 18675691
13 Cahali S, Cahali MB, Lavinsky L, Cahali RB. Hidropisia Endolinfática. In: de Campos CAH, Costa HOO, editors. Tratado de otorrinolaringologia. 1rt ed. São Paulo: Rocca; 2003(02)479–485
14 Bahmad F Jr. Doença/síndrome de Ménière. In: Piltcher OB, da Costa SS, Maahs GS, Kuhl G, authors. Rotinas em otorrinolaringologia. 1rd ed. Porto Alegre: Artamed; 2015:108–121
15 Alexander TH, Harris JP. Current epidemiology of Meniere's syndrome. Otolaryngol Clin North Am 2010;43(05):965–970
16 Kimura RS. Experimental blockage of the endolymphatic sac and duct and its effect on the inner ear of the guinea pig. Ann Otol Rhinol Laryngol 1967;76:664–687
17 Fukuoka H, Takumi Y, Tsukada K, et al. Comparison of the diagnostic value of 3 T MRI after intratympanic injection of GBCA, electrocochleography, and the glycerol test in patients with Meniere's disease. Acta Otolaryngol 2012;132(02):141–145
18 Paparella MM. Pathology of Meniere's disease. Ann Otol Rhinol Laryngol Suppl 1984;112(01):31–35
19 Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandalà M, Newman-Toker DE, Strupp M, Suzuki M, Trabalzini F, Bisdorff A. Criterios diagnósticos de enfermedad de Menière. Documento de consenso de la Bárány Society, la Japan Society for Equilibrium Research, la European Academy of Otology and Neurotology (EAONO), la American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) y la Korean Balance Society [Diagnostic criteria for Menière's disease. Consensus document of the Bárány Society, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology (EAONO), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) and the Korean Balance Society]. Acta Otorrinolaringol Esp 2016 Jan-Feb;67(1):1–7. Spanish. Doi: 10.1016/j.otorri.2015.05.005. Epub 2015 Aug 12. PMID: 26277738
20 Portmann G. Surgical treatment of vertigo by opening of the saccus endolymphaticus. Arch Otolaryngol 1969;89(06):809–815
21 Dandy WE. Ménière's disease: symptoms, objective findings and treatment in forty-two cases. Arch Otolaryngol 1934;20(01):1–30. Doi: 10.1001/archotol.1934.03600010008001
22 Silverstein H, Norrell H, Smouha E, Jones R. Combined retrolab-retrosigmoid vestibular neurectomy. An evolution in approach. Am J Otol 1989 May;10(3):166–169. PMID: 2787602

Aquaporin 4 and its Relationship with Brain Astrocytomas – Literature Review

Aquaporina 4 e sua Relação com Astrocitomas Cerebrais – Revisão da Literatura

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Abstract

Background Aquaporins (AQPs) are a family of membrane proteins that regulate the osmotic permeability of the plasma membrane. There are described in the literature a total of 13 types of Aquaporins in mammals, each with different places of expression. In addition to water, some AQPs allow the passage of glycerol and ammonia, being called Aquaglyceroproteins. In the central nervous system, AQPs 1 and 4 are expressed, being responsible for the water regulation in the blood-brain barrier. These two AQPs are believed to participate in the pathophysiological process that governs the behavior of various CNS diseases, such as trauma and primary tumors. More particularly, there are quite controversial data in the literature on the expression of AQP4 in tumors and its relationship with disease progression and treatment possibility.

Objective This paper aims to perform a literature review on the function and expression of AQP4 in the CNS and primary tumors of this system, to compile what is in the literature on the subject and raise new possible research hypotheses.

Methods The PUBMED platform was used for bibliographic survey using "Aquaporin 4," "expression" and "astrocytomas" as keywords. Articles older than 2008 and articles that did not address AQP4 expression in astrocytomas were excluded. In the selected articles, the following topics were investigated: AQP4 structure, brain and tumor localization, and relationship with peritumoral edema.

Results Regarding the structure and location of AQP4, the literature presents two isoforms of AQP4: M1 and M23. Both form clusters of AQP4 called "orthogonal arrays of proteins - OAPs." In the tumor tissue, the literature shows a decrease in the formation of OAPs and an increase in the expression of both AQP4 isoforms, besides losing their polarity, diffusing through the cytoplasmic membrane. As for the function of AQP4 in

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tumors, AQP4 assists in cell migration and invasion, in addition to participating in cell proliferation and apoptosis. Regarding the relationship with cerebral edema, there are controversial knowledge. Studies have shown that increased AQP4 aggravates cytotoxic edema of tumor cells and, by assisting in cell migration and angiogenesis, indirectly assist in the formation of vasogenic edema by breaking the blood-brain barrier. Other studies, however, point to the increase in AQP4 as a protective mechanism to combat vasogenic edema that occurs in tumor formation. Furthermore, the literature presents a therapeutic proposal in which, by inhibiting AQP4 expression, tumor migration and cerebral edema decrease in rats with glioblastoma.

Discussion As shown in the literature, there is a difference in histopathological structure between high and low grade gliomas. However, there are common changes between them. These common changes could then be used as a factor of severity or evolution of low-grade to high-grade tumors. Moreover, it is not yet possible to perceive the true relationship of AQP4 expression and increased VEGF evolution of peritumoral edema. Finally, it can be hypothesized that since the expression ratio between AQP4 isoforms in normal tissue is greater than in some tumors, the decrease in this ratio is due either to decreased M23 expression or increased of the isoform M1.

Conclusion Further studies are needed to understand the physiology and pathophysiology involving AQP4 in astrocytomas to create effective therapeutic proposals to combat this disease.

Resumo

Introdução As aquaporinas (AQPs) são uma família de proteínas de membrana que regulam a permeabilidade osmótica da membrana plasmática. Existem descritos na literatura um total de 13 tipos de aquaporinas em mamíferos, cada um com diferentes locais de expressão. Além da água, alguns AQPs permitem a passagem de glicerol e amônia, sendo chamados de aquagliceroproteínas. No sistema nervoso central, as AQPs 1 e 4 são expressas, sendo responsáveis pela regulação da água na barreira hematoencefálica. Acredita-se que esses dois AQPs participem do processo fisiopatológico que regula o comportamento de várias doenças do SNC, como trauma e tumores primários. Mais particularmente, há dados bastante controversos na literatura sobre a expressão de AQP4 em tumores e sua relação com a progressão da doença e possibilidade de tratamento.

Objetivo Este artigo tem como objetivo realizar uma revisão da literatura sobre a função e expressão da AQP4 no SNC e tumores primários deste sistema, a fim de compilar o que está na literatura sobre o assunto e levantar novas hipóteses de pesquisa possíveis.

Método A plataforma PUBMED foi utilizada para levantamento bibliográfico utilizando "Aquaporin 4," "expression" e "astrocitomas" como palavras-chave. Artigos com idade superior a 2008 e artigos que não abordaram a expressão de AQP4 em astrocitomas foram excluídos. Nos artigos selecionados, foram investigados os seguintes tópicos: estrutura da AQP4, localização do cérebro e do tumor e relação com o edema peritumoral.

Resultados Em relação à estrutura e localização da AQP4, a literatura apresenta duas isoformas da AQP4: M1 e M23. Ambos formam aglomerados de AQP4 chamados "arranjos ortogonais de proteínas - OAPs." No tecido tumoral, a literatura mostra uma diminuição na formação de OAPs e um aumento na expressão de ambas as isoformas AQP4, além de perder sua polaridade, difundindo através da membrana citoplasmática. Quanto à função da AQP4 nos tumores, a AQP4 auxilia na migração e invasão celular, além de participar da proliferação celular e apoptose. Em relação à relação com o edema cerebral, existem controvérsias. Estudos demonstram que o aumento da AQP4 agrava o edema citotóxico das células tumorais e, auxiliando na migração celular e na angiogênese, auxilia indiretamente na formação de edema vasogênico por quebra da barreira hematoencefálica. Outros estudos, no entanto, apontam para o aumento da

AQP4 como mecanismo protetor para combater o edema vasogênico que ocorre na formação de tumores. Além disso, a literatura apresenta uma proposta terapêutica em que, ao inibir a expressão da AQP4, a migração tumoral e o edema cerebral diminuem em ratos com glioblastoma.

Discussão Como mostrado na literatura, há uma diferença na estrutura histopatológica entre os gliomas de alto e baixo grau. No entanto, existem mudanças comuns entre eles. Estas alterações comuns poderiam então ser usadas como um fator de gravidade ou evolução de tumores de baixo grau a alto grau. Além disso, ainda não é possível perceber a verdadeira relação entre a expressão da AQP4 e o aumento da evolução do VEGF no edema peritumoral. Finalmente, pode-se supor que, como a razão de expressão entre as isoformas de AQP4 no tecido normal é maior do que em alguns tumores, a diminuição dessa razão é devida à diminuição da expressão de M23 ou ao aumento da isoforma M1.

Conclusão: Novos estudos são necessários para compreender a fisiologia e a fisiopatologia da AQP4 em astrocitomas, a fim de criar propostas terapêuticas efetivas para combater essa doença.

Background

There is currently a total of 13 types of Aquaporins in mammals, each with its expression in different body tissues such as red blood cells, lungs, pancreas, kidneys and nervous tissue. All AQPs form tetramers in membranes in which monomers, each of ~30kd molecular size, contain six transmembrane helical domains and two helical segments surrounding cytoplasmic and extra-cellular vestibules. The vestibules are connected by a narrow aqueous pore allowing single-file water transport in which water selectivity is coferred by electrostatic and steric factors.[1] They are proteins that regulate the flow of water into and out of the cell. However, some of the AQPs such as AQP3 and AQP8 also allow the passage of glycerol and ammonia, called aquaglyceroproteins.[2,3] In the central nervous system there is an increase in AQP 1 and AQP 4 in astrocytes submitted to neoplasms and trauma.[4] The structure, function and location of AQPs in the various organs are known. However, there is still to be discovered about the relationship and interaction that these proteins play in the various pathophysiological processes involving such organs. These findings would allow the genesis of new ways to approach pathologies such as neoplasia, especially of the CNS, in which AQP 4 has a great influence, not yet fully known.

Gliomas are the most common central nervous system tumors. Glioblastoma multiforme (GBM) is the most common and malignant brain tumor with high mortality and poor prognosis. The vast majority of patients develop symptoms within ~3 months and die within 8 to 18 months of diagnosis. Less than half live more than 6 months and only 3% have a 2-year survival. Malignant gliomas have a very aggressive and relapsing behavior, giving the patient a very poor prognosis. For this reason, new therapies are needed to change this scenario.[3]

Therefore, the aim of this review is to address the literature on the structure and location of this protein in the CNS, as well as its function and expression in the healthy CNS and brain gliomas. Finally, this study will address the relationship between this protein and peritumoral edema that is present in the literature and the new therapeutic approaches in research.

Methods

The PUBMED database platform was used for consultation using the keywords "Aquaporin 4," "Expression" and "Astrocytoma." The language was used as a selection criterion, preferably choosing articles in Portuguese, Spanish and English. This study included all articles found since 2008, including other systematic reviews. Articles that did not address Aquaporin 4 expression in astrocytomas anywhere in the paper were excluded from this review. In the articles surveyed, the following topics were investigated: AQP4 structure, brain and tumor localization, relationship with edema and relationship with VEGF.

Results

Structure and Location of AQP4 in Brain and Tumors

Aquaporins are a family of integral membrane proteins that regulate the osmotic permeability of the plasma membrane, allowing water to pass through the membrane while blocking entry of ions or charged solutes.[2] It contains 6 transmembrane α-helices, with 2 asparagine-proline and alanine (NPA) loops, each with its cytoplasmic B and extracellular E portion oriented 180 degrees apart.[2] There are a total of 13 types of aquaporins in mammals.[5] In the Brain tissue there are three types of aquaporins: AQP 1, AQP 4 and AQP 9.[6]

AQP4 is usually expressed at the end of astrocyte perivascular cytoplasmic protrusions (►**Fig. 1**), ependimoglia and glia limitans, in the black and gray substance where there is 10 to 15 times more molecular AQP4 than in the rest of brain tissue.[2,4,7–10] AQP4 is also found in the hippocampal

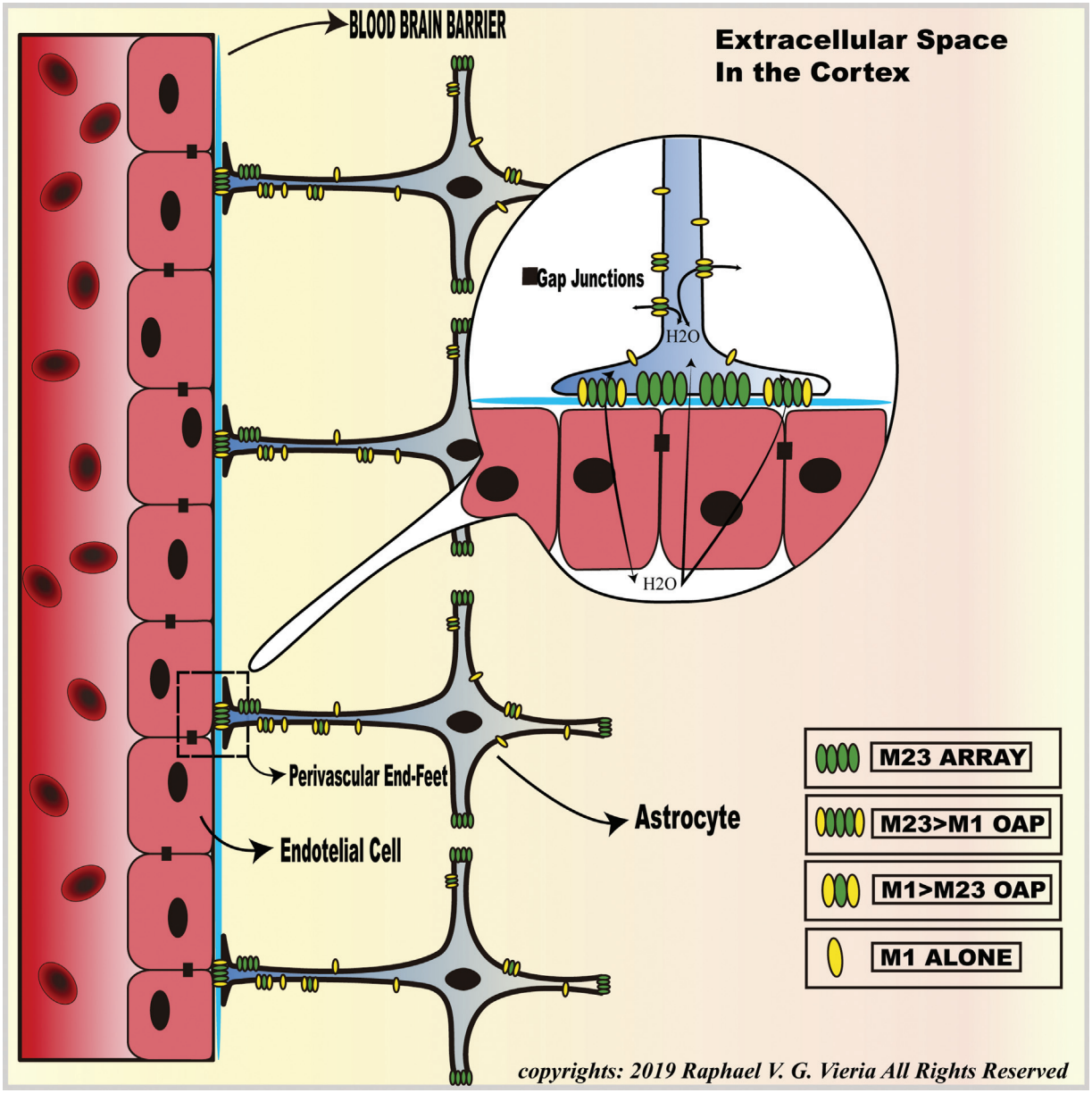

Fig. 1 Extracellular structure and astrocytic interaction with the normal brain blood-brain barrier.

dentate gyrus, medial habenular nucleus, cerebellum, neocortex, and supra-optic and suprachiasmatic nuclei of the hypothalamus.[2] The polarized expression of AQP4 coincides with the location of potassium channels, however, in gliomas, the location is lost and the water channels disperse throughout the cell surface.[11] The protein comes in two different isoforms, M1 and M23, with 22 fewer amino acids.[4] Both isoforms have the same water permeability, but different aggregation properties.[12] With the mixture of the two isoforms and the agrin and dehydroglycan proteins, the so-called Orthogonal Arrays of Particles (OAPs) of different sizes are formed, which are present mainly at the extremities of the astrocyte protrusions[4,13] (►**Fig. 2**). OAPs rich with the presence of the M23 isoform promote the formation of large OAPs with little mobility, standing stationary at the end of the astrocyte perivascular process.[12] M1isoform rich OAPs are small and diffuse freely into the cell membrane, mainly for astrocyte processes, to aid in cell migration[12] (►**Fig. 2**). The M1 isoform can exist alone in the cell, also moving freely through the membrane.[4,12] The isoform M23, when it does not agglomerate with the isoform M1, does so among themselves, forming larger and less mobile clusters.[4,12] Agrine is an extracellular matrix proteoglycan and destroglycan is a component of the dystrophin-destroglycan complex. The agrina connects to the dystrophin-dehydroglycan complex, which in turn connects to OAPs. There complexes also contain the inwardly rectifying potassium channel Kir4.1, a protein involved in spatial buffering of K^+ ions released, because of synaptic activity, into the extracellular space.[14] Noel et al. Showed that this chain of molecules undergoes glioma alterations.[4] The hypothesis that Agrina and destroglycan are responsible for the polarization of AQPs in the vascular extremities of astrocytes has been tested *in vitro*[15] and *in vivo*[4,16]. *In vitro* it has been shown that rats

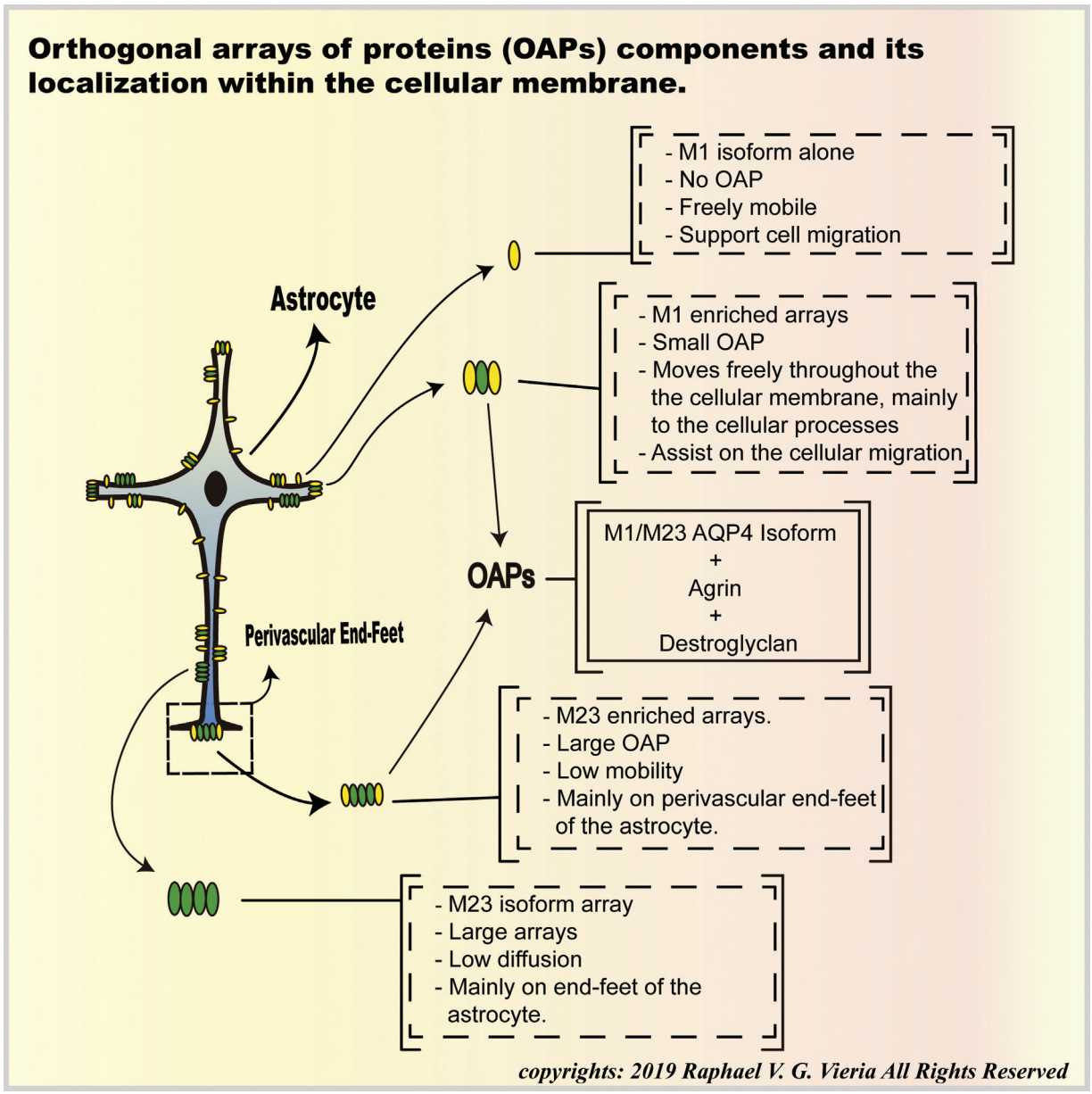

Fig. 2 OAP components and their location in the astrocyte membrane.

lacking agrin undergo alteration of membrane distribution of AQP4.[3] In rats with no dehydroglycan, there was loss of OAPs at the vascular end of the astrocytes, which correlated with down-regulation of AQP4 in the region.[3,4]

In same study, Noel et al showed that astrocytes at the extremities of glioblastomas present the classic star shape with the presence of AQP4 at the vascular end of astrocytic protrusions, the same pattern found in non-tumor astrocytes.[4] In the primary glioblastoma cell membrane, the density of OAPs is small even if there is contact with the basal lamina (►**Fig. 3**). In the relapsing Glioblastoma cell membrane, the occurrence of regular OAPs is also small, and of non-polarized distribution, but with density similar to the parenchyma and membrane area outside the astrocyte protrusion end. This shows the loss of cell polarization of astrocytes during glioma transformation[8] in both primary and recurrent tumors, and in the latter, the density of OAPs is closer to the normal pattern.[4] In addition, tumor regions with greater presence of small blood vessels showed greater immunoreactivity to AQP4 than regions with larger blood vessels[4] (►**Fig. 4**). It is possible to observe the redistribution of AQP4 already in the tumor infiltration zone around the tumor, where the neurovascular functional structure is normal.

Reinforcing the above, Ndoum et al., In 2013,[17] through MRI analysis and immunohistochemistry, showed that low-grade gliomas preserve their astrocyte processes, vascular structure and blood-brain barrier, and there is no significant angiogenesis in the lesion. (►**Fig. 5**). The author explained this fact by the tumor cell's ability to invade healthy tissue and receive nutrients through the phenotypically normal astrocyte structure. The opposite occurs in high grade gliomas. Astrocyte structure and basement membrane are lost around the tumor vasculature. There is diffuse reactivity of

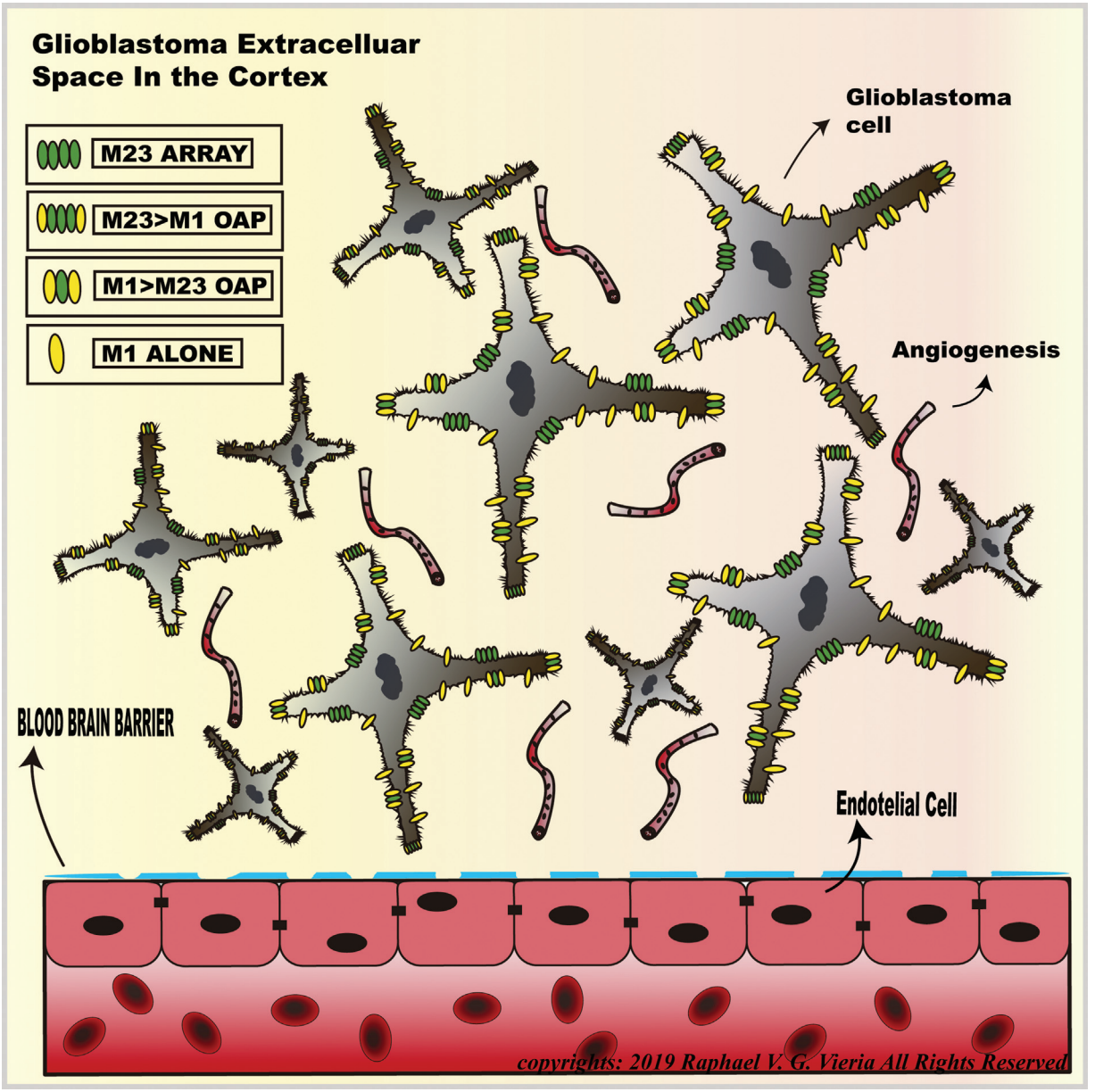

Fig. 3 Astrocyte extracellular structure in Glioblastoma and cellular localization of OAPs - AQP 4.

AQP4 by the tumor and loss of uniformity in AQP4 reactivity where the blood brain barrier is still intact[10] (►**Fig. 3**).

AQP4 Function in Brain and Gliomas

The main function of AQP 4 are to regulate the exchange of intracellular and extracellular water molecules, provide a transportation route for the rapid movement of water, participate in water regulation *in vivo*, and maintain the water balance *in vivo*.[18]

AQP4 is known to participate in the formation of cerebral edema following trauma or other brain diseases.[18] The distribution of AQP4 in the astrocyte cytoplasm suggests that this protein has the function of controlling the flow of water into and out of the brain parenchyma.[2,4,10,19,20] As a bidirectional water channel, AQP 4 facilitates brain water accumulation in cytotoxic edema and clearance of excess brain water in vasogenic and interstitial edema.[1] Moreover, astrocytes are known to express AQP4 in OAPs primarily in cell protrusions. Some of these protrusions involve the basal lamina of the cerebral vessels, fundamentally participating in the maintenance of the blood-brain barrier.[3] The deletion of AQP4 can reduce water permeability through the cell plasma membrane in the brain.[6] In addition to controlling the flow of water into and out of the cell, it has been postulated that AQP 4 actively participates in the cell migration process.[3,9,19] By expelling water, the cell can easily change its morphology. As in gliomas, the expression of aquaporin 4 is increased, the tumor cell has a great capacity for migration and tissue invasion. This hypothesis was tested by Zhao et al.[9] using LN229 glioblastoma cells, in which there is low expression of AQP4, showing low capacity for migration and tissue invasion *in vitro*. LN229 cell chemotaxis, compared with the control group, was lower. In addition to chemotaxis, chemokinesis, which is

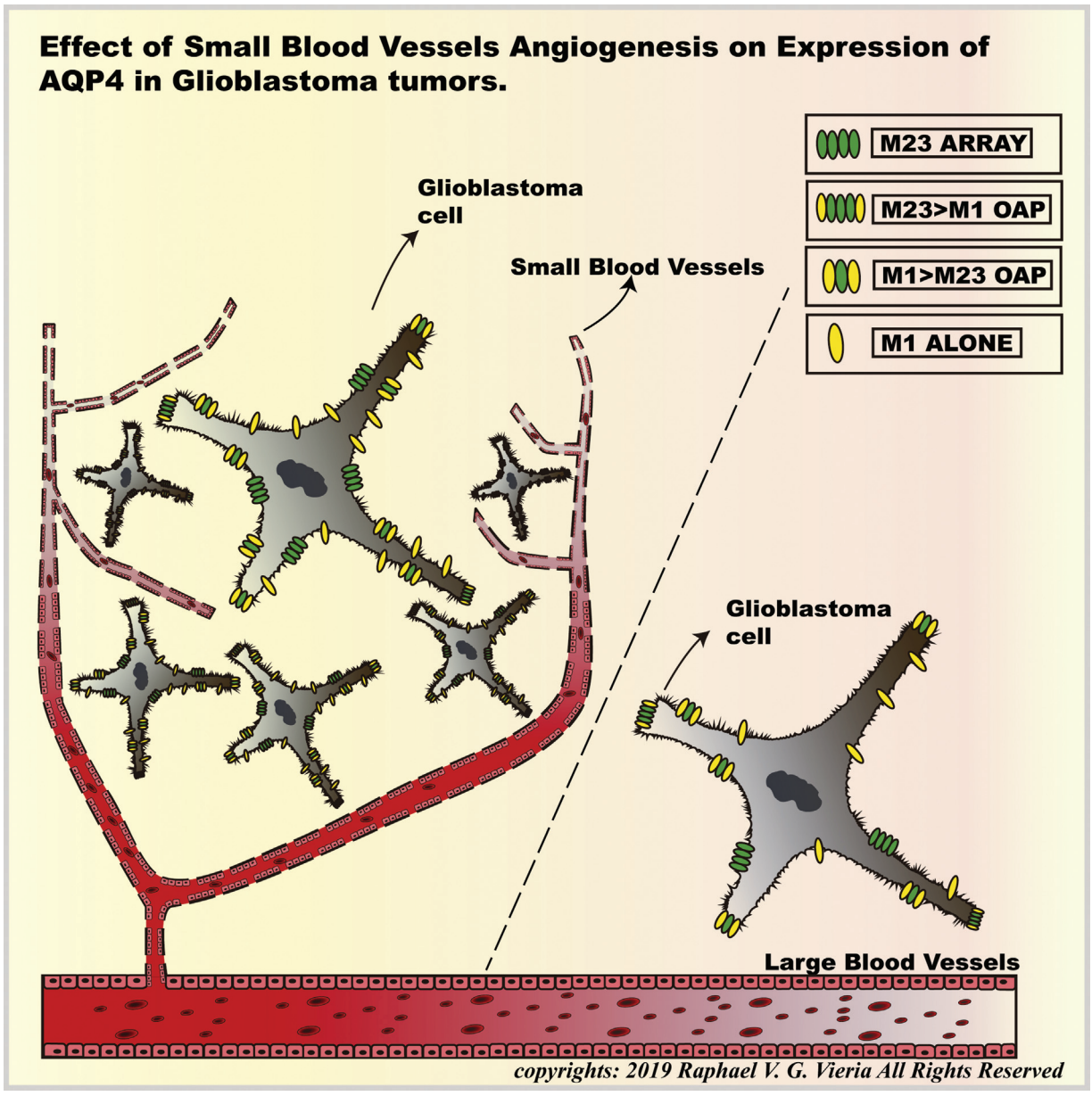

Fig. 4 Effect of neoangiogenesis on AQP4 expression in small OAPs in Glioblastoma.

independent of concentration gradient, was also lower in the group with lower AQP4 expression.[19] Lack of AQP4 seems to change cell morphology. The cell body of LN229 cells became thin and elongated. Reduction of AQP4 decreases the cell's ability to adhere to the substrate due to reduced actin-F protein polymerization. Moreover, these cells showed higher cell-cell adhesion capacity and lower invasion capacity according to the Matrigel Boyden chamber test *(in vitro)*. *In vivo*, the same pattern is repeated. Mice injected with glioblastoma cells without AQP4 showed less cellular invasion than the control group.[19]

Increasing AQP4 expression to some extent may facilitate the reabsorption of water accumulated in the extracellular space, whereas a large increase in AQP4 expression may cause water accumulation in glial cells leading to cell death.[9]

Studies by Ding et al., 2013, showed that AQP4 directly participates in the processes of glioblastoma cell proliferation and apoptosis. By reducing the amount of AQP4 using RNA inhibitor, human glioblastoma cells LN229 and U87 suffered apoptosis and had their replication cycle shortened.[10]

AQP4 Expression in Gliomas

Mou et al.,[21] showed that AQP 4 expression is higher in the peritumoral region than in the tumor itself and in normal brain tissue, besides increasing according to the histological grade of the tumor. In addition, a positive correlation was observed between AQP4 expression with VEGF and HIF-1α. This result differs from that found in older literature, which showed higher protein expression in the center of the tumor.[3] Tan et al.[22] compared MRI images and AQP4 mRNA expression between high-grade and low-grade gliomas. The author found higher mRNA values in high-grade tumors than in low-grade solid tumors, which is consistent with most of the literature.

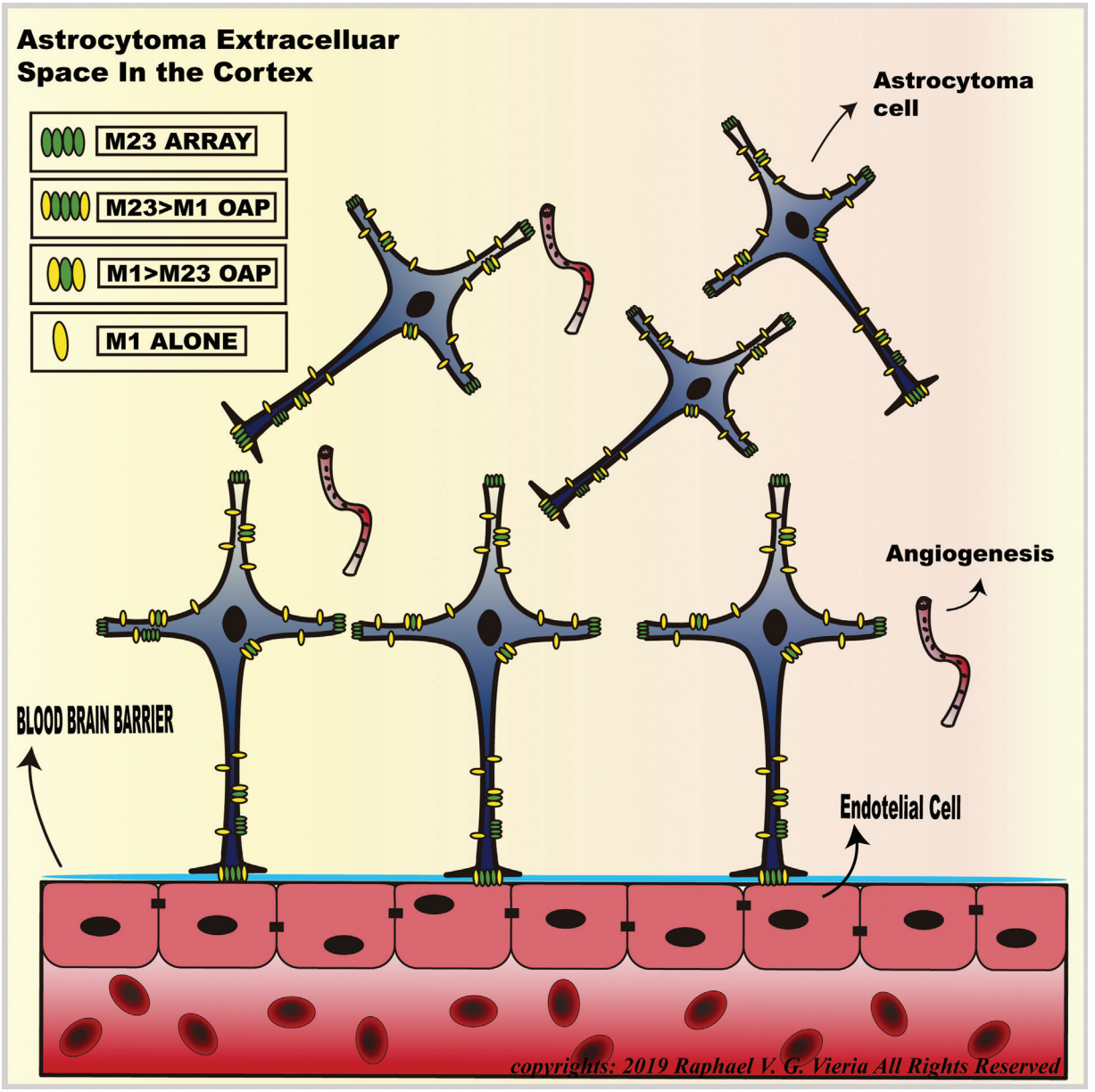

Fig. 5 Astrocyte extracellular structure in astrocytomas and cellular localization of OAPs - AQP 4.

Isoardo et al. compared AQP-4 expression in Glioblastoma multiforme between patients with and without seizures.[23] In his study, the average tumor size among patients with and without seizures was no different, as well as cortical involvement and MRI bleeding. Regarding the expression of AQP-4 by immunohistochemistry, a greater increase in expression was detected in patients with seizures than in those without seizures. The presence of AQP-4 was detected in the GBM cell membrane. In patients with epileptic seizures the distribution of AQP-4 was diffuse or perivascular, while in patients without seizures the immunohistochemistry was undetectable or showed a diffuse pattern of expression.[23] However, by PCR there was no difference in expression between the 2 groups and both showed increased expression of AQP-4.[23] Michael DeLay et al,[24] in 2012, showed that anti-VEGF antibody resistant glioblastomas show higher AQP4 expression. Through electron microscopy, Noel et al., In 2012, confirmed the greater amount of AQP4 in glioblastoma than in control tissue.[4] In the same study, Western blotting results showed that both M1 and M23 isoforms increased expression in the primary tumor. However, in relapsing glioblastoma tissues, AQP4 expression is lower, comparable to control tissue, and with M23 isoform more expressed than M1. In addition, tumor regions with greater presence of small blood vessels showed greater immunoreactivity to AQP4 than regions with larger blood vessels[4] (►**Fig. 3**). While AQP4 expression is increased in glioblastomas, the concentration of OAPs is reduced. According to Noel et al., 2012, this could be explained by the increased expression of the M1 isoform, which does not lead to the formation of dense OAPs (►**Fig. 3**). However, the expression ratio between M1 and M23 forms did not change in glioblastomas.[4] Similarly, Becker et al., 2016, found similar results when performing real-time PCR and electron microscopy to

compare different expression of AQP4 isoforms in different glioma grades. The author found a fall relationship in the presence of OAPs from low to high grade gliomas.[15] However, there was no correlation between tumor malignancy and M1 isoform expression, since this expression was uniform. In fact, there was an increase in M23 isoform expression on average 1.5 higher than M1 isoform, being higher in grade IV gliomas. However, the M23 / M1 ratio in a healthy brain is at least 3.[15] The author concludes, therefore, that the formation of OAPs depends on other mechanisms besides the change of the M23 / M1 isoforms relation.[15]

Contrary to what is shown in the previously mentioned studies, Zhao et al., 2012, observed a pattern of decreased AQP4 expression from grade II to IV gliomas. Their conclusion was that AQP4 expression does not depend entirely on tumor malignancy, but rather on tumor type. However, it has been shown that glioma cells with higher migration capacity show higher AQP4 expression.[9] Moreover, the study also showed that in low-grade gliomas, the concentration of AQP4 in astrocyte perivascular processes is higher than in high-grade gliomas.[9]

To relate radiological characteristics in MRI of gliomas and expression of AQP4, Tan et al., In 2016, compared diffusion imaging of kurtosis (mean kurtosis, radial kurtosis and axial kurtosis) and tension diffusion (mean diffusion) in High and low grade gliomas. Their study showed that there is greater expression of AQP4 in the solid part of high grade gliomas compared with low grade. Moreover, it showed that there is a directly proportional relationship between the mean, radial and axial kurtosis with the expression of AQP4, while the mean diffusion showed an inversely proportional relationship with the expression of AQP4.[25] The study also showed that the mean kurtosis value in the peritumoral edema area is higher in high grade gliomas than in low grade gliomas. This result may have been due to a larger tumor infiltration of the high grade gliomas,[25] which may mean a tumor staging method through imaging.

Wang et al[26] proposed to research the expression of AQP 1 and 4 in the main pediatric brain tumors. Regarding aquaporin 4 in astrocytomas, the author found that high-grade gliomas did not express AQP 4, while there was high protein expression in pilocytic astrocytomas, but with great variability. Houng et al[27] also demonstrated low AQP 4 expression in pilocytic astrocytoma samples, but high expression in low-grade diffuse astrocytoma samples, mainly around the microvasculature and with an intact blood-brain barrier.

AQP-4 Relationship with Edema

Brain edema is typically present in human brain cancers and affects both the course and outcome of pathology, therefore can be considered a prognostic factor.[28] The appearance and effects of edema in clinical progression of brain cancers has been known since long ago in clinical practice. Schoenegger et al. showed shorter survival time after surgery in patients with major peritumoral edema ($\geq$ 1 cm) in MRI.[28]

Cerebral edema is associated with various neurological disorders such as ischemia, trauma and tumor; all leading to increased intracranial pressure and its comorbidities such as herniation and death.[2] Under normal conditions, water moves in and out of the central nervous system, obeying osmotic pressure.[2] There are 3 mechanisms of formation of cerebral edema: cytotoxic, vasogenic and interstitial. Cytotoxic edema results from the disturbance of cellular metabolism, increasing the movement of liquid into the intracellular space. Vasogenic edema occurs due to alteration of the BBB, allowing greater passage of water and macromolecules, accumulating fluid in the extracellular space. Interstitial edema occurs due to an obstruction of the ventricular channels, causing hydrocephalus, in which the accumulated fluid leaks through the periventricular walls.[2] Filippidis et al., 2016, reviews the relationship of aquaporins with cerebral edema. The author points out several studies on the subject such as the reduction of intracranial pressure due to cytotoxic edema in rats without AQP4 expression. Fazzina et al., 2010, demonstrated that treatment with protein kinase C irreversible activator reduces cerebral edema by decreasing AQP4 expression.[29] Besides, AQP 4 deletion in mice reduces cytotoxic brain edema.[30] Yang et al., in 2008, showed that AQP4-overexpressing mice had an accelerated progression of cytotoxic brain swelling on acute water intoxication produced by intraperitoneal water injection. This lad to higher intracranial pressures (ICP). In contrast, ICP was lower in AQP4 knockout mice.[30]

Both benign and malignant tumors produce cerebral edema, which may be due to BBB defect and increased tumor angiogenesis (Papadopoulos et al., 2003). Saaduon et al., 2002, demonstrated that rats without AQP4 with edematous brain tumor showed higher intracranial pressure values and more neurological complications when compared with rats with AQP4, showing a possible protective effect of AQP4.[1] This information contrasts with the study of the same author, 2005, in which AQP4 promotes tumor metastasis by facilitating cell migration and angiogenesis,[1] thus promoting the formation of vasogenic edema.

Isoardo et al. compared the edema rate among patients with GBM who had epileptic seizures and who had no seizures. There was no difference in edema between the two groups and there was no difference between patients with positive and negative immunohistochemical results. The author explains these results by choosing patients with lesions of similar dimensions since the aim of the study was to determine if AQP-4 is related to the onset of epileptic seizures regardless of edema.[23]

The work of Yang et al., 2012, observed the relationship between VEGF and AQP4 in edema formation. By associating AQP4 expression with glioma cells expressing different amounts of VEGF, the author found that there is no difference in AQP4 expression by different amounts of VEGF.[31] However, there is increased expression of AQP4 in tumor tissue with increased VEGF, vascular permeability and water content. The author concludes that VEGF does not directly affect AQP4 expression, but that AQP4 redistribution in glioblastoma cells is a reaction to VEGF-induced vasogenic edema to facilitate resorption of excess fluid.[31]

Mou et al., 2010[21] found that in edema associated with gliomas, AQP4 was also regulated by local osmotic pressure and hypoxia. The degree of peritumoral edema could only be

directly related to AQP4 expression in the peritumoral region of the samples.

The findings in the study by Nduom et al. In 2013 have clinical implications in that the breakdown of the BBB and astrocyte structure may lead to ultrafiltrate leakage through endothelial vessels and cause peritumoral vasogenic edema.[17]

Henker et al., In 2016, related 10 different types of polymorphisms with the preoperative volumetric characteristics of multiform glioblastomas. Using MRI and PCR, the study shows a strong relationship between 4–31G and 131G Aquaporin polymorphism and the ratio of tumor volume to peritumoral edema. The presence of this polymorphism determines lower measured peritumoral edema compared with tumor volume.[32] In situations where there is no polymorphism, the ratio of peritumoral edema to volume showed that the edema was on average twice as large as the tumor volume, and the necrosis area was one quarter of the total tumor volume.[32] AQP4–131G> A is the promoter area of the AQP4 gene. Thus, a change in this area may lead to alteration of AQP4 expression and consequent decrease of water accumulation and reduction of peritumoral edema.[32]

Discussion

Frequently, cell lines or primary cells cultures from glioblastoma are used to measure the cell volume regulation, but many glioma cell lines do not express the water channel proteins. Besides, the majority of freshly isolated glioma cells do not express any of these water channels in vitro in primary cell cultures. However, in glioma tissue, from which the cells were isolate, AQP 4 were detected.[4,13]

Could the occurrence of AQP4 redistribution in the astrocyte plasma membrane already in the tumor infiltration zone suggest an early factor to predict transformation to Glioblastoma? The tumor infiltration zone still has normal neurovascular structure and can be compared with normal tissue.[8] Moreover, the results shown by Nduom et al. 2013, could support the hypothesis that the finding of AQP4 redistribution by astrocytes could be considered as a malignancy factor for the tumor, since low grade tumors preserve their macrostructure more similar to normal tissue. High-grade tumors, on the other hand, do not preserve the blood-brain barrier, as well as diffuse expression of AQP4 throughout the cell membrane, even near vascularization.[17]

Increasing AQP4 expression to some extent may facilitate the reabsorption of water accumulated in the extracellular space, whereas a large increase in AQP4 expression may cause water accumulation in glial cells leading to cell death.[9] The expression level of AQP4 correlates with the level of cerebral edema. One of the factors that contribute to the maintenance of the blood-brain barrier is the concentration of AQP4 in perivascular astrocyte processes.[9,20] Electron microscopy has shown that gap junction opens in the high-grade astrocytoma microsvasculature. This, added to the loss of polarization of AQP4 in astrocytes can lead to increased edema.[9] Conversely, as a result of the breakdown of the blood-brain barrier, the redistribution of AQP4 into glioblastoma cells may act as a countermeasure to vasogenic edema. This reinforces the hypothesis that AQP may be involved in the dynamics of edema formation or resolution. The fact is that there is more about brain edema formation than just AQP4. It has been shown that Na^+-K^+-Cl^- cotransportes 1, matrix-metalloproteinase 9, thrombin, substance P and chemokine receptors are also involved in the process.[33]

Increasing the amount of AQP4 expression in higher VEGF tumor tissue[31] could explain the greater amount of AQP4 found in tumor cells near small vessels compared with large vessels,[4] since VEGF is the main modulator of angiogenesis. The author himself concluded that there is no statistical relationship between VEGF value and AQP4 expression, but these two factors could be physiopathologically involved.

The process of cellular invasion of malignant gliomas is complex and multifactorial. In addition to increased cellular mobility, other mechanisms such as reduced substrate and neighbor cell adhesion and extracellular matrix degradation are also involved. The role of aquaporin 4 in these mechanisms is not yet fully understood. The same could also be seen in the systematic review by Lan et al.[3]

Although the biomolecular behavior of brain gliomas has not been clarified, treatment methods are a target of research. Nico et al., 2009, found that the combination of chemotherapy and radiotherapy reduces AQP4 expression[4,8] and restores cell polarization.[8] It has also been shown that LN229 glioblastoma cells show lower AQP4 expression. As a result, these cells showed lower capacity for migration and tissue invasion.[8] Thus, the use of AQP4 inhibitory therapies for the treatment of cerebral gliomas would be possible. Ding et al., 2013 showed this possibility by using AQP4 inhibitory RNA in human glioblastoma cells causing apoptosis of these cells.[10] Another proposed idea is the use of AQP4-specific antibody linked with toxin to selectively damage AQP 4-expressing glioblastoma cells.[6] The use of curcumin to attenuate brain edema is also proposed, as one of its effects is the reduction of expression of AQP 4 and 1.[34]

In addition to molecular therapies, noninvasive evaluation methods for gliomas are being studied. The study of Tan et al.[22] correlates mean diffusion coefficient values obtained by serial MRI images between high and low grade gliomas and AQP4 mRNA expression. The study shows higher AQP4 expression in high grade tumors and a directly proportional relationship between AQP4 expression and mean diffusion values in solid parts of the tumor. However, there was no relationship between the diffusion coefficients for the peritumoral edema region. The author believes that the redistribution of AQP4 in the cell surface of high grade gliomas is responsible for the high values of mean diffusion coefficient, showing greater water flow in the solid region of these tumors. Such imaging study could serve as a new form of assessment of staging and expression of AQP in astrocytomas.

No studies were found in the literature associating the expression value of AQP4 with patient follow-up or survival after surgery. Such studies could show some relationship from which there was a predictive value of patient survival after possible surgery. Moreover, most of the laboratory studies had the limitation of a small sample space, impairing the impact or the statistical weight of the results.

Conclusion

With this review it is possible to realize that there is not only one mechanism that influences the relationship between AQP4 expression and the pathophysiology of cerebral gliomas. Some of these mechanisms have already been identified and hypotheses of therapeutic intervention are being tested. Given the morbidity and mortality of the disease, more studies are needed in the area, not only of therapeutic proposals, but also proposals to promote patient comfort or avoid submitting unnecessary procedures.

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References

1 Verkman AS. Aquaporins in clinical medicine. Annu Rev Med 2012;63(01):303–316
2 Filippidis AS, Carozza RB, Rekate HL. Aquaporins in Brain Edema and Neuropathological Conditions. Int J Mol Sci 2016;18(01): 55
3 Lan Y-L, Wang X, Lou J-C, Ma X-C, Zhang B. The potential roles of aquaporin 4 in malignant gliomas. Oncotarget 2017;8(19): 32345–32355http://www.oncotarget.com/fulltext/16017 cited2018Oct25 [Internet]
4 Noell S, Wolburg-Buchholz K, Mack AF, et al. Dynamics of expression patterns of AQP4, dystroglycan, agrin and matrix metalloproteinases in human glioblastoma. Cell Tissue Res 2012;347 (02):429–441
5 Saito M, Tanaka H, Sasaki M, Kurose H, Nakahata N. Involvement of aquaporin in thromboxane A2 receptor-mediated, G 12/13/RhoA/NHE-sensitive cell swelling in 1321N1 human astrocytoma cells. Cell Signal 2010;22(01):41–46
6 Wang J, Feng L, Zhu Z, et al. Aquaporins as diagnostic and therapeutic targets in cancer: how far we are? J Transl Med 2015;13(01):96http://www.translational-medicine.-com/content/13/1/96 cited2019Sep23 [Internet]
7 Ding T, Gu F, Fu L, Ma Y-J. Aquaporin-4 in glioma invasion and an analysis of molecular mechanisms. J Clin Neurosci 2010;17(11): 1359–1361
8 Nico B, Mangieri D, Tamma R, et al. Aquaporin-4 contributes to the resolution of peritumoural brain oedema in human glioblastoma multiforme after combined chemotherapy and radiotherapy. Eur J Cancer 2009;45(18):3315–3325
9 Zhao W-J, Zhang W, Li G-L, Cui Y, Shi Z-F, Yuan F. Differential expression of MMP-9 and AQP4 in human glioma samples. Folia Neuropathol 2012;50(02):176–186
10 Ding T, Zhou Y, Sun K, et al. Knockdown a water channel protein, aquaporin-4, induced glioblastoma cell apoptosis. PLoS One 2013; 8(08):e66751
11 Yool AJ, Brown EA, Flynn GA. Roles for novel pharmacological blockers of aquaporins in the treatment of brain oedema and cancer. Clin Exp Pharmacol Physiol 2010;37(04):403–409
12 Smith AJ, Jin B-J, Ratelade J, Verkman AS. Aggregation state determines the localization and function of M1- and M23-aquaporin-4 in astrocytes. J Cell Biol 2014;204(04):559–573
13 Noell S, Ritz R, Wolburg-Buchholz K, Wolburg H, Fallier-Becker P. An allograft glioma model reveals the dependence of aquaporin-4 expression on the brain microenvironment. PLoS One 2012;7(05): e36555
14 Maugeri R, Schiera G, Di Liegro CM, Fricano A, Iacopino DG, Di Liegro I. Aquaporins and Brain Tumors. Int J Mol Sci 2016;17(07):1029
15 Fallier-Becker P, Nieser M, Wenzel U, Ritz R, Noell S. Is Upregulation of Aquaporin 4-M1 Isoform Responsible for the Loss of Typical Orthogonal Arrays of Particles in Astrocytomas? Int J Mol Sci 2016;17(08):1230
16 Noell S, Fallier-Becker P, Deutsch U, Mack AF, Wolburg H. Agrin defines polarized distribution of orthogonal arrays of particles in astrocytes. Cell Tissue Res 2009;337(02):185–195
17 Nduom EK, Yang C, Merrill MJ, Zhuang Z, Lonser RR. Characterization of the blood-brain barrier of metastatic and primary malignant neoplasms. J Neurosurg 2013;119(02):427–433
18 Li Y, Hu H, Liu J, Zhu Q, Gu R. Effects of aquaporin 4 and inward rectifier potassium channel 4.1 on medullospinal edema after methylprednisolone treatment to suppress acute spinal cord injury in rats. Acta Cir Bras 2018;33(02):175–184
19 Ding T, Ma Y, Li W, et al. Role of aquaporin-4 in the regulation of migration and invasion of human glioma cells. Int J Oncol 2011;38 (06):1521–1531
20 Wolburg H, Noell S, Fallier-Becker P, Mack AF, Wolburg-Buchholz K. The disturbed blood-brain barrier in human glioblastoma. Mol Aspects Med 2012;33(5-6):579–589
21 Mou K, Chen M, Mao Q, et al. AQP-4 in peritumoral edematous tissue is correlated with the degree of glioma and with expression of VEGF and HIF-alpha. J Neurooncol 2010;100(03):375–383
22 Tan Y, Zhang H, Wang XC, Qin JB, Wang L. The value of multi ultra high-b-value DWI in grading cerebral astrocytomas and its association with aquaporin-4. Br J Radiol 2018;91(1086):20170696
23 Isoardo G, Morra I, Chiarle G, et al. Different aquaporin-4 expression in glioblastoma multiforme patients with and without seizures. Mol Med 2012;18(01):1147–1151
24 DeLay M, Jahangiri A, Carbonell WS, et al. Microarray analysis verifies two distinct phenotypes of glioblastomas resistant to antiangiogenic therapy. Clin Cancer Res 2012;18(10):2930–2942
25 Tan Y, Zhang H, Zhao R-F, Wang X-C, Qin J-B, Wu X-F. Comparison of the values of MRI diffusion kurtosis imaging and diffusion tensor imaging in cerebral astrocytoma grading and their association with aquaporin-4. Neurol India 2016;64(02):265–272
26 Wang D, Owler BK. Expression of AQP1 and AQP4 in paediatric brain tumours. J Clin Neurosci 2011;18(01):122–127
27 Hong CS, Ho W, Piazza MG, Ray-Chaudhury A, Zhuang Z, Heiss JD. Characterization of the blood brain barrier in pediatric central nervous system neoplasms. J Interdiscip Histopathol 2016;4(02): 29–33
28 Schoenegger K, Oberndorfer S, Wuschitz B, et al. Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma? Eur J Neurol 2009;16(07):874–878
29 Fazzina G, Amorini AM, Marmarou CR, et al. The protein kinase C activator phorbol myristate acetate decreases brain edema by aquaporin 4 downregulation after middle cerebral artery occlusion in the rat. J Neurotrauma 2010;27(02):453–461
30 Yang B, Zador Z, Verkman AS. Glial cell aquaporin-4 overexpression in transgenic mice accelerates cytotoxic brain swelling. J Biol Chem 2008;283(22):15280–15286
31 Yang L, Wang X, Zhen S, Zhang S, Kang D, Lin Z. Aquaporin-4 upregulated expression in glioma tissue is a reaction to glioma-associated edema induced by vascular endothelial growth factor. Oncol Rep 2012;28(05):1633–1638
32 Henker C, Kriesen T, Fürst K, et al. Effect of 10 different polymorphisms on preoperative volumetric characteristics of glioblastoma multiforme. J Neurooncol 2016;126(03):585–592
33 Thrane AS, Rangroo Thrane V, Nedergaard M. Drowning stars: reassessing the role of astrocytes in brain edema. Trends Neurosci 2014;37(11):620–628
34 Wang BF, Cui ZW, Zhong ZH, et al. Curcumin attenuates brain edema in mice with intracerebral hemorrhage through inhibition of AQP4 and AQP9 expression. Acta Pharmacol Sin 2015;36(08):939–948

Cerebral Aspergillosis in an Immunocompetent Patient after COVID-19 Infection

Aspergilose Cerebral em Paciente Imunocompetente após Infecção por COVID-19

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Abstract

Fungal brain abscesses are an uncommon condition in the immunocompetent population, especially due to the etiologic agent Aspergillus sp. The emerging coronavirus disease 2019 (COVID-19) pandemic brought about neurological manifestations that were previously little known, caused by the direct manifestations of the virus, as well as by the therapy itself, with hospitalization and use of corticosteroids. This manuscript highlights the need for attention in the management of patients with neurological disorders and history of COVID-19 infection. In the current paper, we report the case of a patient without comorbidities who presented multiple brain abscesses caused by Aspergillus fumigatus, after infection by Severe Acute Respiratory Syndrome Coronavírus 2 (SARS-CoV-2).

Keywords

- neuroaspergillosis
- brain abscess
- COVID-19
- aspergillosis

Resumo

Abscessos cerebrais fúngicos são uma condição incomum na população imunocompetente, especialmente quando provocada pelo agente etiológico Aspergillus sp. A epidemia emergente do novo coronavírus (COVID-19) trouxe acometimentos neurológicos até então pouco conhecidos, ocasionados pelas manifestações diretas do vírus, como também pela própria terapia, com internação e uso de corticoesteróides. Este manuscrito destaca a necessidade de atenção no manejo de pacientes com alterações neurológicas e história de infecção pelo vírus. No presente trabalho, relatamos o caso de um paciente sem comorbidades que apresentava múltiplos abscessos cerebrais causados por Aspergillus fumigatus, após infecção pelo SARS-CoV-2.

Palavras-chave

- neuroaspergilose
- abscesso Encefálico
- COVID-19
- aspergilose

Introduction

Cerebral aspergillosis is a rare infectious condition that accounts for ~ 5% to 10% of all fungal infections of the central nervous system (CNS).[1]

The incidence of patients diagnosed with this pathology has increased in recent years due to the rise in the number of solid organ and bone marrow transplants, consequently increasing the immunosuppressed population.[2] Other immunosuppressive states that present the risk of developing

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the disease are AIDS, alcohol abuse, diabetes, and hematologic diseases with neutropenia.[3,4]

The reports of patients with an intact immune system who manifest this infection in the brain are rare. However, when reviewing in detail the history of these patients, it is possible to identify that there was some factor promoting transient immunosuppression, such as the use of chemotherapy, high doses of corticosteroids or poor glycemic control.[5]

In the present paper, we report the case of a man with no previous comorbidities whose only immunosuppression factor in his history was the use of corticosteroids for the treatment of coronavirus disease 2019 (COVID-19).

Case Report

A 64-year-old male rural worker, previously healthy, started to experience changes in his mental state with bradypsychism and ideomotor apraxia. He had a history of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for $\sim$ 2 months, with hospitalization in another service. According to the discharge report, he did not need ventilatory support but received a course of corticosteroid therapy with dexamethasone during the 7-day period he was hospitalized and for another 12 days after discharge. Since then, he started to have a lack of glycemic control, and treatment with metformin was started.

Due to the progression of the neurological condition, he was admitted to a local hospital, and underwent an investigation with brain magnetic resonance imaging (MRI) scans that showed multiple lesions in both cerebral hemispheres, characterized by annular contrast enhancement and diffusion restriction, suggesting brain abscesses (►**Fig. 1**). Empirical treatment was started with vancomycin, ceftriaxone, metronizadole, and dexamethasone 4 mg 4 times a day for the vasogenic edema caused by the lesions.

He was transferred to the neurosurgery service of our hospital with a proposal for a surgical approach to the brain injuries. The antibiotic therapy regimen was expanded to meropenem and vancomycin. We performed a complementary investigation with serology for HIV, hepatitis B, and C, all of which were negative. Chest X-ray (►**Fig. 2**) and transthoracic echocardiography did not identify abnormalities. A stereotaxic biopsy of one of the lesions was then performed with the aspiration of purulent content (►**Fig. 3**).

He remained hospitalized in the Intensive Care Unit (ICU) postoperatively, receiving empirical antibiotic therapy until we received the results of the cultures. He was discharged to the ward on the second postoperative day, in good clinical condition. The results of the pathological examination and

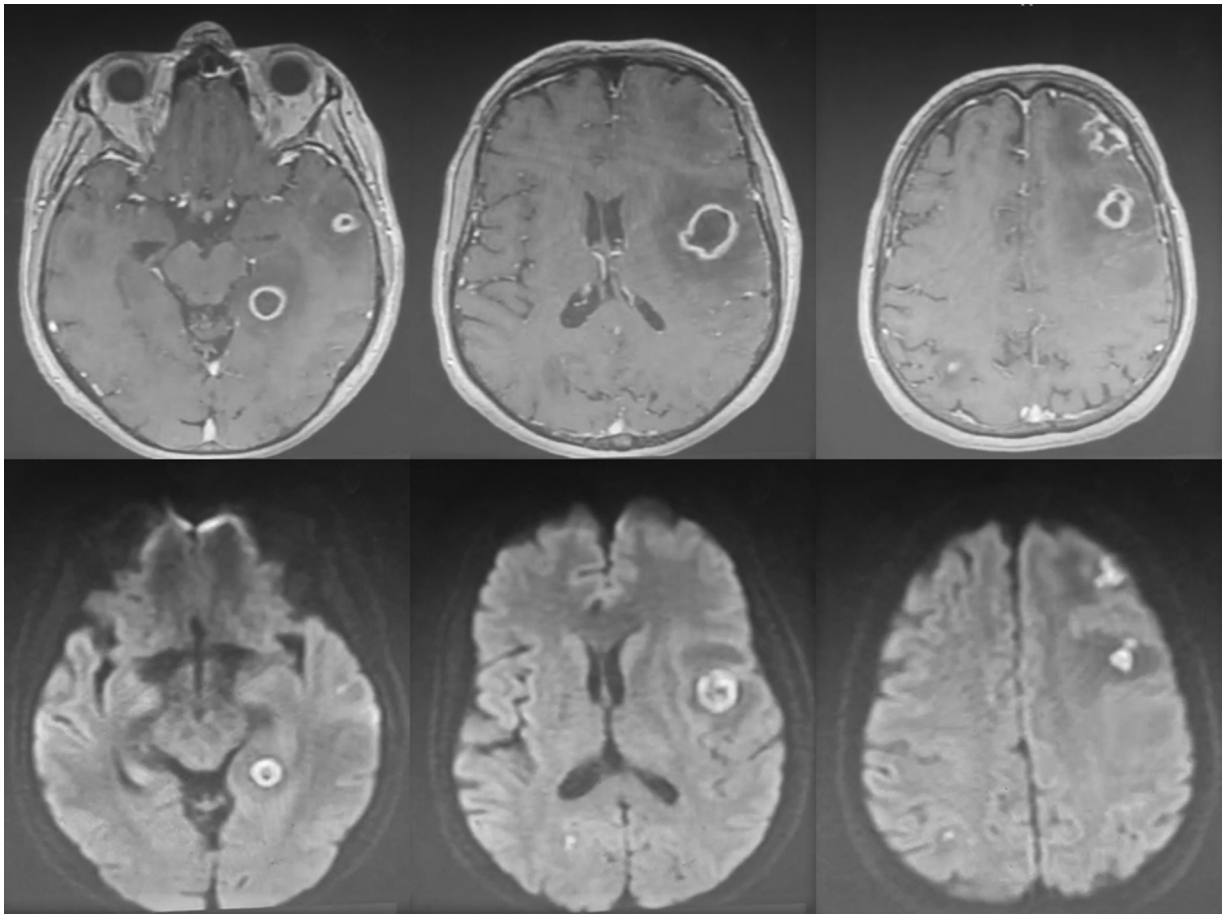

Fig. 1 Brain magnetic resonance imaging (MRI) scan showing\ multiple hypointense brain lesions with a halo of enhancement and surrounding edema on a T1-weighted image (above). Diffusion-weighted imaging (DWI) (below) showing hyperintense lesions.

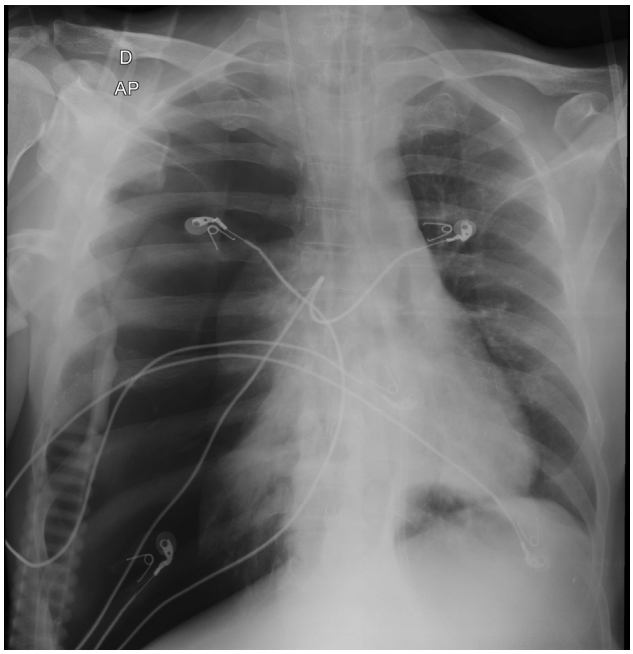

Fig. 2 Chest X-ray without visible changes suggestive of aspergillus pneumonia.

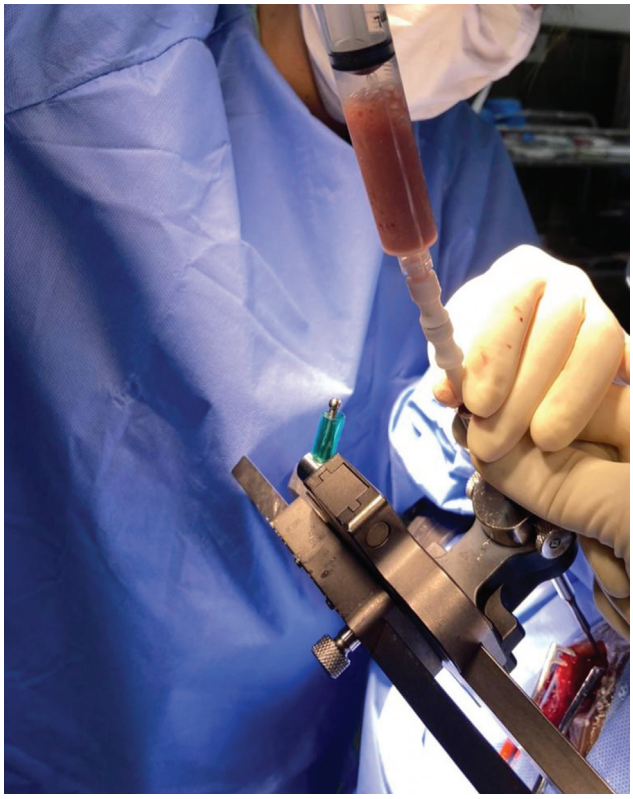

Fig. 3 Intraoperative macroscopic aspect of the aspirate of one of the brain lesions.

cultures were available on the fifth day after surgery, and were compatible with a fungal infection, and *Aspergillus fumigatus* was identified as the etiological agent (►**Fig. 4**). Endovenous voriconazole was indicated.

On the seventh day after surgery, his neurological condition worsened, and he experienced sudden sensorium alteration. An emergency cranial computed tomography (CT) scan was performed, which showed recurrence of the lesion that had been surgically aspirated and important cerebral edema with midline deviation (►**Fig. 5**). As the patient's score on the Glasgow Coma Scale (GCS) was of 3 and bilateral mydriasis had no reactivity, we did not indicate a new surgical approach. After two days of hospitalization in the ICU, the criteria to determine brain death were met.

Discussion

After the respiratory tract, the brain is the site most affected by invasive aspergillosis.[4] The main etiological agent is *A. fumigatus*, with cases of infection by *A. nidulans, A. terreus*, or *A. flavus*[3,4] Presentations in the CNS can be due to meningitis, granulomatous reaction with abscess, or vasculopathy.[1] Aspergillus hyphae have tropism for vessels and can produce thrombosis, infarction, hemorrhagic changes, or mycotic aneurysms.[3,6] Meningeal lesions usually represent contamination by contiguity after infection of the paranasal sinuses, mastoiditis, trauma, or neurosurgery.[2] Parenchymal abscesses are most commonly located in the cerebral hemispheres; however, they may also present in the basal ganglia, corpus callosum, thalamus, or perforating artery territory, suggesting hematogenous dissemination.[2,3]

The clinical presentation is variable, and localized neurological manifestations may be observed. Ruhnke et al.[3] reviewed the results of 4 studies on clinical manifestations of cerebral aspergillosis,[7–10] totaling 90 patients. The most common symptoms were persistent fever, changes in mental status, and seizures.[3] Headache, vomiting, and papilledema with signs of intracranial hypertension may also be observed.

The MRI findings are similar to a common pyogenic abscess, with a hypodense lesion on T1, hyperdense on T2, ring contrast-enhancing, surrounding cerebral edema, and with diffusion restriction. The analysis of the cerebrospinal fluid (CSF) usually shows pleocytosis with a slight increase in protein, and the aspergillus antigen, galactomannan, can be found.[1,11]

The definitive diagnosis is histopathological; however, it is usually not possible to perform a surgical approach to obtain material for analysis, given the severity that many patients present.[3]

The treatment commonly employed involves a combined approach of surgical evacuation and prolonged antifungal administration.[4,12–14] There is no consensus regarding the best surgical strategy, since most studies[2,4,6,7] are small retrospective series. However, the most adopted approach in cases of location in an eloquent area is minimally-invasive aspiration by the stereotaxic method or by neuronavigation. In cases in which resection is feasible, a more extensive surgery should be performed.[1]

The first-line antifungal therapy consists of voriconazole; however, there are reports[1,4,15] of successful treatments with new-generation azole agents, liposomal amphotericin B, caspofungin, or micafungin. The proposed duration of the

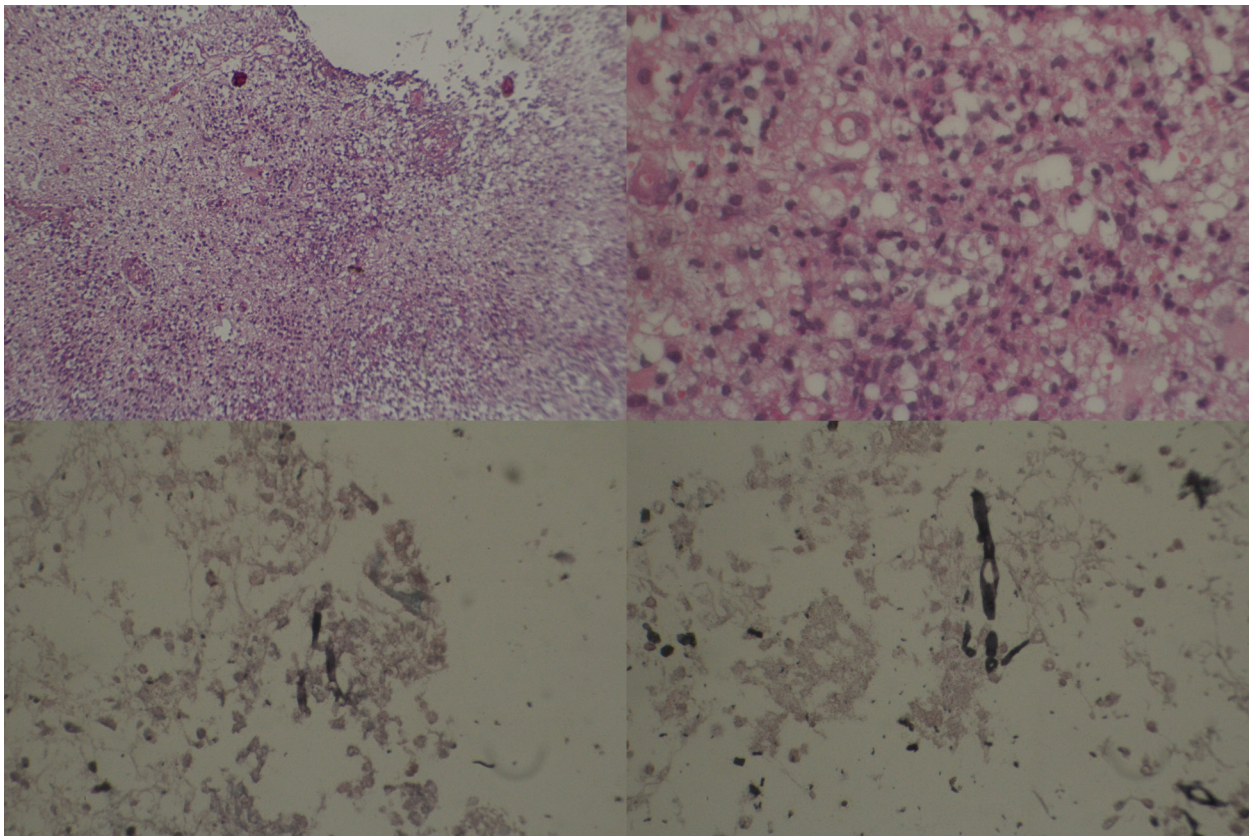

Fig. 4 Microscopic analysis sowing inflammatory infiltrate permeated by multiple neutrophils in hematoxylin and eosin (H&E) staining (above). Below we can see *Aspergillus fumigatus* hyphae in Grocott silver stain.

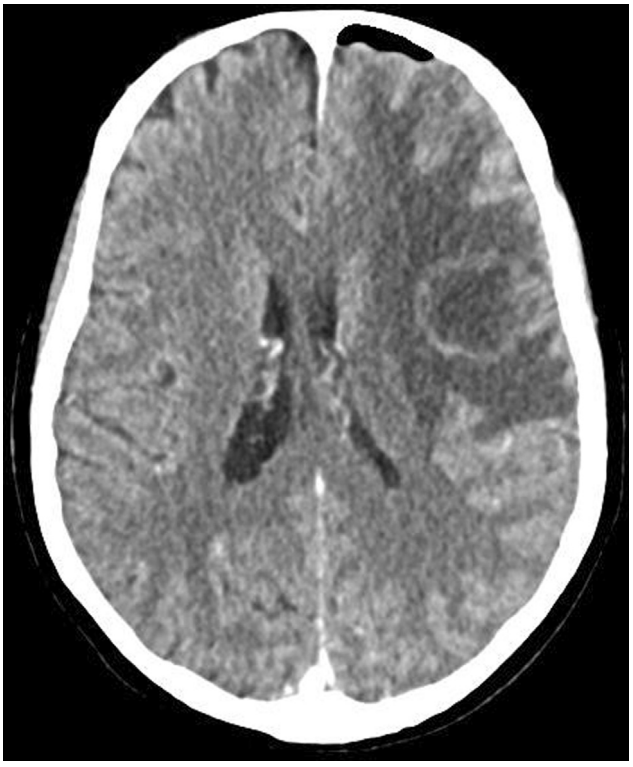

Fig. 5 Head computed tomography scan performed on an urgent basis after the patient's neurological worsening. We can see the permanence of hypodense content with annular contrast uptake, perilesional edema, and midline shift.

treatment varies in the literature and can be influenced by the type of surgery performed. Shorter treatment regimens are employed in cases in which total lesion resection has been performed, with some institutions describing 6 months of therapy with satisfactory results. In cases of subtotal resection, a regimen of 12 to 18 months is advocated.[1]

Despite the appropriate therapy, the disease has an unfavorable prognosis, with reported mortality rates of 10% to 20% in immunocompetent patients, and of 85% to 100% in immunosuppressed patients.[2]

Conclusion

In the case herein reported, an important factor in the previous pathological history was the recent infection by COVID-19. Despite being a disease that has emerged recently, there are already several studies on the manifestations of the virus in the CNS. Neurological involvement may be secondary to the systemic proinflammatory state that may develop in some infected patients, with a predisposition to endothelial dysfunction and prothrombotic events.[16] There are also changes directly caused by the presence of the virus in the nervous system, explained by the binding of viral proteins to neuronal and glial receptors, leading to viral encephalitis, meningoencephalitis, Guillain-Barré syndrome, and seizures.[17]

Fungal brain abscess in an immunocompetent patient was probably a consequence of a combination of factors such as

hospitalization, microvascular alterations caused by the virus, and prolonged use of corticosteroids. We found sparse similar reports in our research,[18,19] which enabled us to raise the hypothesis that despite being a rare condition, it can also be a poorly-recognized change, due to the severity that many patients evolve with the need for ventilatory support and high doses of sedatives, making it difficult to diagnose neurological changes.

A postmortem study would enable a better understanding of the pathophysiological mechanisms responsible for brain involvement; however, this was not an option accepted by the patient's family.

Informed Consent

The patient's family consented to the presentation of the case for submission to the journal.

Conflict of Interests

The authors have no conflict of interest to declare.

References

1 Ellenbogen JR, Waqar M, Cooke RP, Javadpour M. Management of granulomatous cerebral aspergillosis in immunocompetent adult patients: a review. Br J Neurosurg 2016;30(03):280–285
2 Ma Y, Li W, Ao R, et al. Central nervous system aspergillosis in immunocompetent patients: Case series and literature review. Medicine (Baltimore) 2020;99(44):e22911
3 Ruhnke M, Kofla G, Otto K, Schwartz S. CNS aspergillosis: recognition, diagnosis and management. CNS Drugs 2007;21(08): 659–676
4 Spapen H, Spapen J, Taccone FS, et al; AspICU Study Investigators. Cerebral aspergillosis in adult critically ill patients: a descriptive report of 10 patients from the AspICU cohort. Int J Antimicrob Agents 2014;43(02):165–169
5 Stevens DA, Melikian GL. Aspergillosis in the 'nonimmunocompromised' host. Immunol Invest 2011;40(7-8):751–766
6 Louati I, Zaouali J, Azzouz O, et al. [Cerebral aspergillosis in immunocompetent patients: three case reports]. Rev Neurol (Paris) 2009;165(11):957–961
7 Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. Ann Neurol 1985;18(05):574–582
8 Hagensee ME, Bauwens JE, Kjos B, Bowden RA. Brain abscess following marrow transplantation: experience at the Fred Hutchinson Cancer Research Center, 1984-1992. Clin Infect Dis 1994;19 (03):402–408
9 Boes B, Bashir R, Boes C, Hahn F, McConnell JR, McComb R. Central nervous system aspergillosis. Analysis of 26 patients. J Neuroimaging 1994;4(03):123–129
10 Jantunen E, Volin L, Salonen O, et al. Central nervous system aspergillosis in allogeneic stem cell transplant recipients. Bone Marrow Transplant 2003;31(03):191–196
11 Tattevin P, Jauréguiberry S, Gangneux JP. [Cerebral aspergillosis]. Rev Neurol (Paris) 2004;160(5 Pt 1):597–605
12 Beraldo D, Guerra R, Alvarenga V, Crepaldi L. Surgical Treatment Alone of Cerebral Aspergillosis in Immunocompetent Patient. J Neurol Surg A Cent Eur Neurosurg 2016;77(05):452–456
13 Marzolf G, Sabou M, Lannes B, et al. Magnetic Resonance Imaging of Cerebral Aspergillosis: Imaging and Pathological Correlations. PLoS One 2016;11(04):e0152475
14 Wang RX, Zhang JT, Chen Y, Huang XS, Jia WQ, Yu SY. Cerebral aspergillosis: a retrospective analysis of eight cases. Int J Neurosci 2017;127(04):339–343
15 Hall WA. Improving outcomes in cerebral aspergillosis. World Neurosurg 2014;82(1-2):e139–e140
16 Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther 2020;12(01):69
17 Satarker S, Nampoothiri M. Involvement of the nervous system in COVID-19: The bell should toll in the brain. Life Sci 2020; 262:118568
18 Gupta V, Singh P, Sukriti K. Fungal brain abscess in a post COVID-19 patient. BMJ Case Rep 2021;14(09):e246319
19 Hakamifard A, Hashemi M, Fakhim H, Aboutalebian S, Hajiahmadi S, Mohammadi R. Fatal disseminated aspergillosis in an immunocompetent patient with COVID-19 due to Aspergillus ochraceus. J Mycol Med 2021;31(02):101124

Ewing Sarcoma in the Sciatic Nerve: Case Report

Sarcoma de Ewing no Nervo Ciático: Relato de Caso

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Abstract

Ewing sarcoma (ES) is a malignant neoplasm that affects bones and soft tissues, usually in young patients. Currently, ES is grouped with other tumors that share the same histological and genotypic characteristics, forming the Ewing Sarcoma Family of Tumors (ESFT), which includes ES of bone, extraosseous ES (peripheral neuroepithelioma), Askin tumor, and peripheral primitive neuroectodermal tumor (PNET). Its origin in peripheral nerves is extremely rare, making its diagnosis and treatment very challenging. We describe a case of a 27-year-old male with extraosseous ES originating in the sciatic nerve, which was surgically removed, and discuss the difficulties encountered in the management of this patient.

Keywords
- Ewing sarcoma
- peripheral nerves
- primitive neuroectodermal tumor

Resumo

O sarcoma de Ewing (SE) é uma neoplasia maligna que acomete ossos e partes moles, geralmente em pacientes jovens. Atualmente, o SE é agrupado com outros tumores que compartilham as mesmas características histológicas e genotípicas, formando os Tumores da Família do Sarcoma de Ewing (TFSE), que incluem o SE ósseo, o SE extraósseo (neuroepitelioma periférico), o tumor de Askin, e o tumor neuroectodérmico primitivo (TNEP) periférico. Sua origem em nervos periféricos é extremamente rara, o que torna o seu diagnóstico e tratamento um grande desafio. Descrevemos o caso de um homem de 27 anos com SE extraósseo originário no nervo ciático, que foi removido cirurgicamente, e discutimos as dificuldades encontradas no manejo desse paciente.

Palavras-chave
- sarcoma de Ewing
- nervos periféricos
- tumor neuroectodérmico primitivo

Introduction

Ewing sarcoma (ES) is an uncommon malignant neoplasm that most often affects the bones of children and adolescents.[1] In ~ 25% of the cases, ES can originate in soft tissues.[2] Currently, these tumors are included in the Ewing Sarcoma Family of Tumors (ESFT), because they have the same histological and genotypic characteristics.[3] Extraosseous ES

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originating from peripheral nerves is very rare. We present a case of extraskeletal ES originating in a young patient's sciatic nerve, and discuss the great challenge of treating patients with this pathology.

Case Report

A 27-year-old, Caucasian, male patient presented with complaints of progressive loss of strength in the left foot with 13 months of evolution associated with pain in the back of the left thigh with proximal and distal irradiation. Upon examination, the patient was in good general condition, with café-au-lait patches on the abdominal wall, without other stigmata of type-1 neurofibromatosis. He had a palpable mass between the middle and lower thirds of the left posterior thigh, of ~ 5 cm, mobile, non-pulsatile, painful, and with a positive Tinel sign. Upon auscultation, no murmurs were perceived. The neurological examination showed grade-0 strength for hallux extension and dorsiflexion, and grade-1 strength for left foot eversion, and tactile and painful hypoesthesia on the side of the left leg and foot. An MRI scan identified an oval, circumscribed tumor in the left sciatic nerve, without affecting the neighboring planes, without signs of edema surrounding it, with annular uptake of contrast suggestive of schwannoma/neurofibroma (►**Fig. 1**). An electroneuromyography exam identified axonal involvement of the left sciatic/common fibular nerve, with signs of denervation in muscles innervated by the left fibular nerve. Surgical treatment was applied, with access to the back of the left thigh to expose the sciatic nerve and the origin of the left tibial and common fibular nerves. A tumor of ~ 7 cm in length and 3.2 cm in its largest diameter was identified, located in the final and lateral portions of the sciatic nerve and in the origin of the common fibular nerve (►**Fig. 2**). Circumferential dissection was performed, and no adherence to neighboring tissues was observed. The tumor was easily detached from the tibial nerve. The fascicle where the tumor originated was identified in the final portion of the sciatic nerve. Electrical stimulation showed no response. The tumor was resected en bloc, sparing a fascicle of the common fibular nerve. The sectioned fascicle was reconstructed with two 8-cm sural nerve cables each. A pathology examination described a malignant neoplasm of small cells of high cellularity and with areas of necrosis. The immunohistochemical study was negative for antibodies CKAE1/AE3, S100, actin, desmin, CK7, synaptophysin and positive for CD 99, CD 56, vimentin, BcL-2, and rarely positive in neoplastic cells for EMA. A total of 70% of the neoplastic cells were positive for Ki67. (►**Fig. 3**). These characteristics were compatible with the diagnosis of peripheral primitive neuroectodermal tumor (PNET)/Ewing sarcoma. Clinical staging was performed with chest tomography, whole-body scintigraphy and bone marrow biopsy, without evidence of metastatic tumor. Chemotherapy started with vincristine, doxorubicin, and cyclophosphamide (VDC) alternated with ifosfamide and etoposide (IE) every two weeks (the VDC-IE combination) for a year of treatment, complemented with local radiotherapy. The treatment was well tolerated by the patient, who evolved with improved sensitivity in the left leg and foot, improved strength in dorsiflexion of the foot (M3) and non-functional improvement in hallux extension and eversion of the foot (M1). The

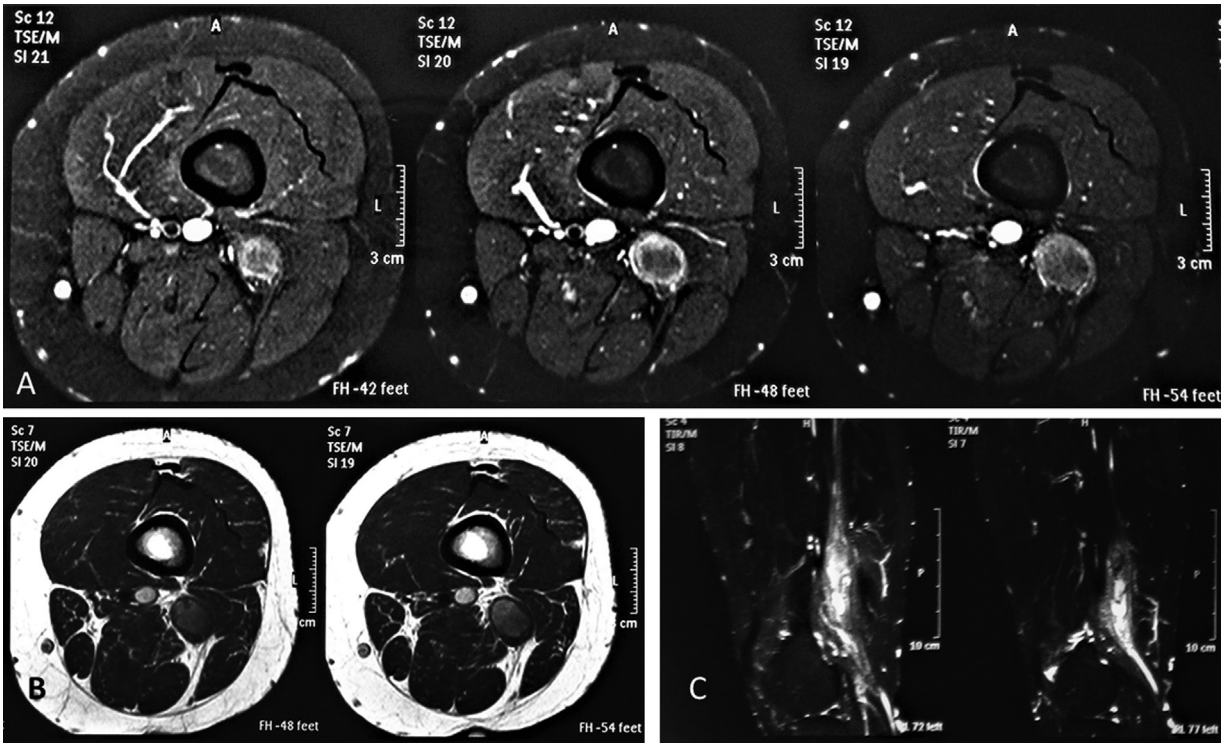

Fig. 1 (**A**) T1-weighted magnetic resonance imaging (MRI) in axial sections showing uptake of the contrast, more intense at the periphery. (**B**) T1-weighted MRI in axial sections showing regular lesion of well-defined limits without invasion of neighboring planes and without surrounding edema. (**C**) T2-weighted short tau inversion recovery (STIR) MRI in sagittal sections showing sciatic nerve damage in the topography of its bifurcation.

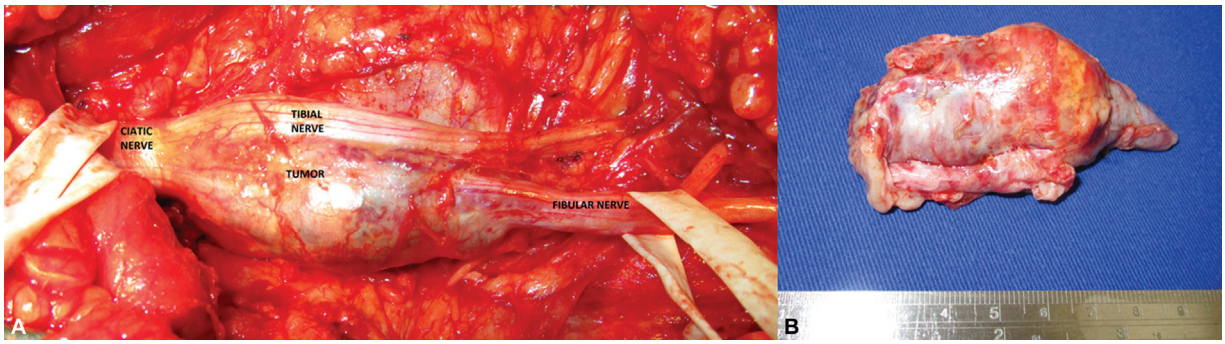

Fig. 2 (**A**) Photograph of the surgical field showing a tumor on the left sciatic nerve, affecting its circumscribed fibular portion, with no signs of invasion of neighboring tissues. (**B**) Photograph of the 7-cm long surgical specimen.

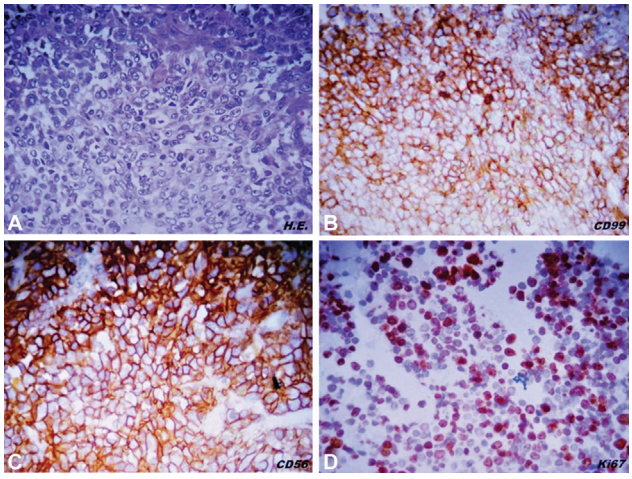

Fig. 3 (**A**) Slide stained with hematoxylin and eosin showing a small, blue, regular cell tumor with large nuclei and fine chromatin; magnification: 20X. (**B**) CD99 positivity on immunohistochemistry; magnification: 20X. (**C**) Positivity for CD56 on immunohistochemistry; magnification: 20X. (**D**) Positivity for K_i 67 in 70% of tumor cells; magnification: 20X

signs of neurological recovery started with 10 months of the surgery, and progressed until the 14th postoperative month, after which it stopped, despite the physical therapy treatment for 24 months after the surgery. In the first postoperative year, the patient underwent local radiological control with MRI scans every 3 months and chest tomography every 6 months; in the second postoperative year, the patient underwent local radiological control with MRI scans every 6 months. The last local control with MRI was performed at the 28th postoperative month, without evidence of local recurrence (►**Fig. 4**). The patient is still being followed-up by oncology.

Discussion

Ewing sarcoma (ES) is a rare malignancy that affects bones and soft tissues. Its incidence was of 2.93 per 1 million inhabitants in the United States between 1973 and 2004.[2] Despite this, it is the second most common malignant bone tumor in children and adolescents. The peak incidence occurs at 10 and 20 years of age, being uncommon after 30 years of age. Ewing sarcoma has a predilection for the male sex (male/female ratio: 1.3–1.5:1), it is more frequent in Caucasians than in Asians and Africans or African-Americans.[4] Currently, ES is grouped with other tumors that share the same histological and genotypic characteristics, forming ESFT, which includes ES of bone, extraosseous ES (peripheral neuroepithelioma), Askin tumor, and peripheral PNET.[5] From the histological point of view, the ESFT presents as small, round, blue cell tumors when stained with hematoxylin and eosin (H&E), homogeneous, containing varying amounts of necrosis. Additional findings of rosettes and pseudorosettes, indicating neuronal differentiation, may also be observed in cases of PNET.[6] Another characteristic common to ESFT is the t (11; 22) (q24; q12) translocation

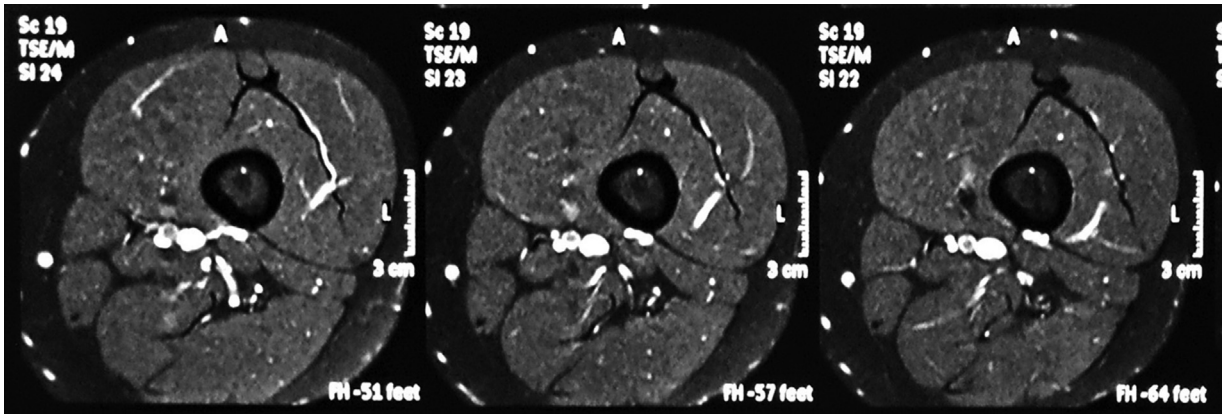

Fig. 4 T1-weighted contrast-enhanced MRI 28 months after the surgical treatment, with no signs of local recurrence.

that produces a chimeric gene called *EWSR1-FLI1*, which occurs in ~ 85% of tumors. Another fusion, which occurs in 10% of cases, is the result of translocation t (21:22) (q22; q12), which generates the *EWSR1-ERG* gene. These fusions encode chimeric proteins that function as aberrant oncogenic factors. On immunohistochemistry, about 90% of ESFT cases are positive for CD99, a membrane glycoprotein product of the *MIC2* gene.[5–7] There are hypotheses about the origin of these tumors, among them: the theory of parental mesenchymal stem cells, and that of an origin in a primitive nerve cell or in the postganglionic cholinergic neurons of the parasympathetic system; however, the true progenitor cell of these tumors remains unknown.[1,3,7]

About 25% of cases of ESFT are in soft tissues, affecting patients between 10 and 30 years of age, with a peak incidence at 20 years of age. The most frequent sites include the chest wall, the paravertebral musculature, the lower extremities, and the retroperitoneal space.[4] Head and neck involvement is uncommon.[8] There are reports of renal[9] and pancreatic ES,[10] and cases of ESFT originating in nerves are very rare. It is interesting to note that probably the first report of ESFT was made by Stout et al. in 1918, who described a case of tumor originating in the ulnar nerve, composed of round and undifferentiated cells that exhibited the formation of rosettes, and that the concept of neuroepithelioma was later proposed.[11] Reports of other cases of ESFT originating in the nerves are scarce. Nesbitt and Vidone[12] reported a case of PNET of the sciatic nerve in a 6-year-old patient; Martins et al.[13] reported a case of PNET arising from a branch of the sciatic nerve in a 17-year-old female patient; and Akeyson et al.[14] described a case of PNET originating in the median nerve of an elderly patient. They are typically fast-growing tumors, usually painful. Approximately 1/3 of the cases of extraosseous ES have distant metastases at the time of the initial diagnosis, but extraskeletal ES is considered a systemic lesion since its presentation, even without documented metastasis. The initial assessment is performed with MRI scans of the affected site followed by a biopsy of the tumor with a needle or an open procedure. Staging is performed with chest tomography and whole-body scintigraphy. The performance of bone marrow biopsy in the initial stage is controversial. Among the factors with the worst prognosis, the existence of metastasis in the initial evaluation is the most significant. Patients with a single lung metastasis have a slightly more favorable prognosis than those with metastases in other regions. Other unfavorable prognostic factors include age > 10 years, tumor larger than 8 cm or with volume > 200 mL, central lesions (in the pelvis or spine), and low response to chemotherapy.[15]

The treatment consists of systemic chemotherapy associated with local treatment (surgery and/or radiotherapy). The drugs proven effective for the treatment of ESFT include doxorubicin, cyclophosphamide, vincristine, actinomycin-D, ifosfamide, and etoposide. Currently, the regimen with VDC-IE is the protocol used in countries in North America and in many countries in Europe. The response to chemotherapy is an important prognostic factor. For local control, radical surgical resection is the best option. For those cases in which the lesion cannot be completely removed or in the absence of an adequate safety margin, local radiotherapy would be indicated.[2,4,6,11,15]

Considering the aforementioned information, the ideal case, the one with the best prognosis, is the patient with a localized tumor, who responds adequately to chemotherapy, and its complete surgical resection with a safety margin is possible. This raises many questions in relation to the case herein described. First, the initial diagnostic hypothesis of an ESFT, due to the rarity of the pathology, would have never been considered a probable option. There are no elements in the clinical history and neurological examination that can differentiate it from other more frequent peripheral nerve tumors such as schwannomas and neurofibromas. Second, the subsidiary exams did not provide elements that would suggest the diagnosis of this illness. The anatomical MRI exam was accurate in relation to the tumor topography and its limits, but insufficient to indicate the histological type and detect signs of malignancy. In a study comparing the characteristics of neurofibromas and malignant tumors of nerve sheaths on MRI, Wasa et al.[16] described some aspects that could facilitate differentiation: mass dimensions, since malignant lesions tend to be larger; the perilesional enhancement; the perilesional edema zone; and the intralesional cystic lesion. The presence of two or more of these characteristics suggested a malignant tumor of the nerve sheath with a sensitivity of 61% and specificity of 90%. There are no studies comparing the aspects of nerve ESFT MRI with those of other tumors. Using the data found by Wasa et al.[16] in our case, we would not find any indication of malignancy, because the tumor dimensions were not bulky, and there was no perilesional edema or intralesional cystic lesion. The observed peripheral enhancement can be found in neurofibromas and even in schwannomas.[17,18] Nerve tractography and functional MRI can be valuable tools to differentiate between benign and malignant tumors of the peripheral nerves; however more studies are needed to elucidate this question.[19–21]

Another aspect to be discussed is the surgical treatment performed. Most peripheral nerve tumors are composed of benign lesions, and the incidence of malignant peripheral nerve tumors is of around 0.001%. In a brief review, Ball and Biggs[22] described the steps of the surgical management of benign peripheral nerve tumors (BPNTs). Clinical history and propedeutic with appropriate electrophysiological and imaging tests are essential. Percutaneous biopsies of nerve tumors should be avoided, as there is a risk of nerve damage, of spread of tumor cells through the needle path, and of formation of scars that can hinder complete lesion resection. The general principles of BPNT surgical resection include adequate exposure of the lesion, including the healthy proximal and distal portions of the affected nerve, tumor inspection and intraneural dissection to identify and separate uninvolved fascicles, and electrical stimulation to identify functional fascicles. The treatment protocol for ESFT advises to initially perform a tumor biopsy to confirm the diagnosis, followed by neoadjuvant chemotherapy to observe the response. After these steps, local treatment with radical surgery with a safety margin and/or radiation therapy are indicated. In the case herein reported, we changed the order recommended in the treatment protocol for ESFT: the

surgical treatment preceded the other treatments, and this was due to a failure in the preoperative diagnosis. How this will affect the patients prognosis remains to be seen. Another aspect of the surgical treatment to be discussed is the reconstruction of the affected fascicles with a sural nerve graft. Had the diagnosis of ESFT been known, reconstruction with a graft at this time might have been contraindicated because there would be a need for radical resection with a safety margin, although there are no data in the literature to specifically guide this situation. On the other hand, it is interesting to observe the neurological evolution of this patient. Historically, the functional prognosis of patients with traumatic sciatic nerve injuries in the fibular portion or lesions in the common fibular nerve that require graft reconstruction is not favorable, especially in those cases in which the use of long grafts was necessary.[23,24] Kim et al.[25] evaluated the result of the surgical treatment of traumatic fibular nerve injuries and observed that, in those in which reconstruction with a graft larger than 6 cm was necessary, a good functional result occurred in only 44% of cases. In the case herein reported, in addition to the use of grafts for reconstruction, there was a need for local control with radiotherapy, as tumor resection was not performed with a safety margin, and exposure to prolonged chemotherapy with multiple drugs, especially vincristine, which is known to cause sensory-motor neuropathy. The effects of radiation on the peripheral nerves and the possibility of postirradiation neuropathy are well known,[26,27] but there is insufficient data regarding the influence of radiotherapy on nerves reconstructed with a graft. Even in this context, the patient described presented some degree of neurological recovery, especially sensitivity, indicating that there is possibility of nerve regeneration. Therefore, the case herein described offers the possibility of discussing several issues regarding malignant tumors of peripheral nerves, such as the difficulty in establishing the preoperative diagnosis, the limitation of imaging tests to differentiate benign from malignant lesions, and, therefore, the adequate surgical management of these injuries.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Croci AT, Camargo OP, Oliveira NRB. Tratamento cirúrgico do sarcoma de Ewing: avaliação oncológica e funcional. Rev Bras Ortop 1996;31:909–918
2 Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol 2010;11 (02):184–192
3 Pereira RJS, Araújo R, Araújo SCP, et al. Sarcoma de Ewing extraósseo. Arquivos Brasileiros de Ciências da saúde 2010;35:65–68
4 Iwamoto Y. Diagnosis and treatment of Ewing's sarcoma. Jpn J Clin Oncol 2007;37(02):79–89
5 Zagar TM, Triche TJ, Kinsella TJ. Extraosseous Ewing's sarcoma: 25 years later. J Clin Oncol 2008;26(26):4230–4232
6 Davis LE, Malempati S. Ewing sarcoma in adolescentes and Young adults:diagnosis and treatment. Clin Oncol Adolesc Young Adults 2014;4:21–31
7 Rani PSV, Shyamala K, Girish HC, Murgod S. Pathogenesis of Ewing sarcoma: A review. Journal of Advanced Clinical & Research Insights 2015;2:164–168
8 Martínez NV, Rosas DC, Alba LM, et al. Sarcoma de Ewing extraósseo em cabeza y cuello:revisión de la literatura a propósito de um caso. Res Esp Cir Oral Maxilofac 2017;39(02):105–112
9 Alonso AH, Gárate MM, Amo FH, et al. Sarcoma de Ewing renal primário. Arch Esp Urol 2011;64(07):636–639
10 Komforti MK, Sokolovskaya E, D'Agostino CA, Benayed R, Thomas RM. Extra-osseous Ewing sarcoma of the pancreas: case report with radiologic, pathologic, and molecular correlation, and brief review of the literature. Virchows Arch 2018;473(03):361–369
11 Ozaki T. Diagnosis and treatment of Ewing sarcoma of the bone: a review article. J Orthop Sci 2015;20(02):250–263
12 Nesbitt KA, Vidone RA. Primitive neuroectodermal tumor (neuroblastoma) arising in sciatic nerve of a child. Cancer 1976;37 (03):1562–1570
13 Martins RS, Siqueira MG, Moraes OJS, et al. Tumor neuroectodérmico primitivo periférico originado em ramo do nervo ciático. Braz Neurosurg 2002;21(3–4):116–119
14 Akeyson EW, McCutcheon IE, Pershouse MA, Steck PA, Fuller GN. Primitive neuroectodermal tumor of the median nerve. Case report with cytogenetic analysis. J Neurosurg 1996;85(01):163–169
15 Gaspar N, Hawkins DS, Dirksen U, et al. Ewing Sarcoma: Current Management and Future Approaches Through Collaboration. J Clin Oncol 2015;33(27):3036–3046
16 Wasa J, Nishida Y, Tsukushi S, et al. MRI features in the differentiation of malignant peripheral nerve sheath tumors and neurofibromas. AJR Am J Roentgenol 2010;194(06):1568–1574
17 Lee SK, Kim JY, Lee YS, Jeong HS. Intramuscular peripheral nerve sheath tumors: schwannoma, ancient schwannoma, and neurofibroma. Skeletal Radiol 2020;49(06):967–975
18 Bhargava R, Parham DM, Lasater OE, Chari RS, Chen G, Fletcher BD. MR imaging differentiation of benign and malignant peripheral nerve sheath tumors: use of the target sign. Pediatr Radiol 1997; 27(02):124–129
19 Filler AG, Kliot M, Howe FA, et al. Application of magnetic resonance neurography in the evaluation of patients with peripheral nerve pathology. J Neurosurg 1996;85(02):299–309
20 Filler A. Magnetic resonance neurography and diffusion tensor imaging: origins, history, and clinical impact of the first 50,000 cases with an assessment of efficacy and utility in a prospective 5000-patient study group. Neurosurgery 2009;65(4, Suppl) A29–A43
21 Chhabra A, Thakkar RS, Andreisek G, et al. Anatomic MR imaging and functional diffusion tensor imaging of peripheral nerve tumors and tumorlike conditions. AJNR Am J Neuroradiol 2013; 34(04):802–807
22 Ball JR, Biggs MT. Operative steps in management of benign nerve sheath tumors. Neurosurg Focus 2007;22(06):E7
23 Samardzić MM, Rasulić LG, Grujicić DM. Results of cable graft technique in repair of large nerve trunk lesions. Acta Neurochir (Wien) 1998;140(11):1177–1182
24 Roganovic Z. Missile-caused complete lesions of the peroneal nerve and peroneal division of the sciatic nerve: results of 157 repairs. Neurosurgery 2005;57(06):1201–1212, discussion 1201–1212
25 Kim DH, Murovic JA, Tiel RL, Kline DG. Management and outcomes in 318 operative common peroneal nerve lesions at the Louisiana State University Health Sciences Center. Neurosurgery 2004;54 (06):1421–1428, discussion 1428–1429
26 Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. Radiother Oncol 2012;105(03):273–282
27 Gikas PD, Hanna SA, Aston W, et al. Post-radiation sciatic neuropathy: a case report and review of the literature. World J Surg Oncol 2008;6(06):130

Stroke Mimics – Glioblastoma Presenting with Hemorrhage after Thrombolysis: Case Report

Stroke mimics – Glioblastoma apresentando hemorragia após trombólise: Relato de caso

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Abstract

Background Stroke is a clinical syndrome characterized by a sudden-onset neurological deficit of vascular cause. Stroke-like clinical symptoms that are later found to have nonvascular disorders have been termed stroke mimics (MIM), and their incidence ranges from 1.3 to 25% in patients not treated with thrombolytic therapy. Eventually, intravenous thrombolysis of MIM may occur.

Case Description We describe a 74-year-old woman with abrupt global aphasia who received thrombolytic therapy after the presumed diagnosis of acute ischemic stroke. She gradually improved despite the finding of an asymptomatic left temporal hematoma on the computed tomography (CT) scan. Two months later, she presented with a new focal neurological deficit and was diagnosed with a glioblastoma in the topography of the previous bleeding.

Conclusion This case highlights the rare occurrence of hemorrhage after thrombolysis in patients with MIM.

Keywords
- stroke mimics
- glioblastoma
- thrombolysis
- complications

Resumo

Introdução O acidente vascular encefálico (AVC) é uma síndrome clínica caracterizada por déficit neurológico de início súbito. Casos nos quais a sintomatologia é semelhante aos AVCs e que, posteriormente, são identificados como distúrbios não vasculares, foram denominados de *stroke mimics*, cuja incidência varia entre 1,3 e 25% em pacientes diagnosticados com AVC. Eventualmente, pode ocorrer trombólise intravenosa de *stroke mimics*.

Descrição do caso Descrevemos o caso de uma mulher de 74 anos com afasia global abrupta que recebeu terapia trombolítica após o diagnóstico presumido de AVC isquêmico. A paciente apresentou melhora gradual dos sintomas apesar do achado na tomografia computadorizada (TC) de crânio de um hematoma temporal esquerdo

Palavras-chave
- stroke mimics
- glioblastoma
- trombólise
- complicações

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assintomático. Dois meses depois, a paciente apresentou novo déficit neurológico focal e foi diagnosticada com glioblastoma na topografia do sangramento anterior.
Conclusão Este caso destaca a rara ocorrência de hemorragia após trombólise em paciente portador de glioblastoma e com diagnóstico inicial de AVC isquêmico.

Introduction

Cerebral neoplasms are a known cause of stroke mimics (MIM).[1] Approximately 5% of the patients diagnosed with brain tumors are diagnosed at the initial presentation with stroke, and 12% of the patients initially diagnosed with stroke are ultimately given the diagnosis of brain tumor. Glioblastoma (GBM) manifesting with an apoplectic presentation occurs at an estimated frequency of 4%.[2] We report a case of intratumoral hemorrhage after intravenous (IV) thrombolysis in a patient with glioblastoma mimicking stroke.

Case Report

A 74-year-old Caucasian woman presented with acute-onset global aphasia. The patient had no significant prior medical history and was not under medication. On admission, vital signs were unremarkable. Carotid and cardiac auscultations were normal. Pulses were full and symmetrical in both the upper and lower limbs.

On admission, her National Institute of Health Stroke Scale (NIHSS) score was 06. Her brain computed tomography (CT) demonstrated subtle mass effect in the left temporal region, which was attributed to an acute stroke (►**Fig. 1A**). She received intravenous tissue plasminogen activator (IVt-PA) within 3 hours of the onset of her symptoms. The patient gradually improved despite the finding of an asymptomatic left temporal lobe hemorrhage (►**Fig. 1B**). She was discharged without deficits. One month after discharge, she went through surgical treatment of an unruptured anterior communicating artery aneurysm and was discharged uneventfully.

Two months later, she returned to our clinic with a 3-week history of mental confusion, right hand weakness, and speech disturbance. Upon neurological examination, she presented subtle facial asymmetry, grade 4 strength in the distal right upper limb according to the modified scale of the Medical Research Council, and discrete right hemibody hyperreflexia, with no other signs of pyramidal release. The patient was submitted to contrast-enhanced magnetic resonance imaging (MRI), which demonstrated an expansive lesion in the left temporal lobe, suggesting a malignant tumor (►**Fig. 1C**). The patient underwent brain biopsy, and the histologic analysis revealed a glioblastoma. She developed progressive neurological deterioration and died 32 days after surgery.

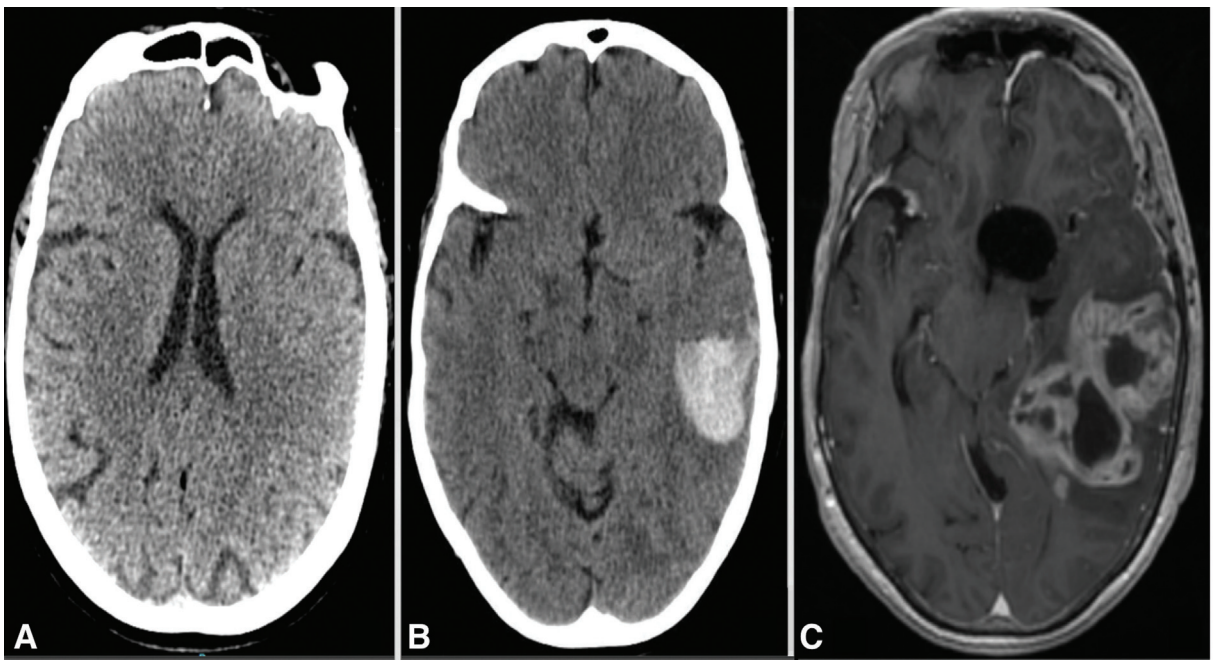

Fig. 1 (**A**) Nonconstrast CT at presentation demonstrating subtle mass effect in the left temporal lobe, with little asymmetry of the lateral ventricles. (**B**) Nonconstrast CT at presentation demonstrating left temporal lobe hemorrhage. (**C**) MRI of the brain, axial view, T1-weighted, post-gadolinium, demonstrates a large lesion in the left frontotemporal region, with necrosis and typical ring-like enhancement suggestive of malignant brain tumor. The image also shows field distortion due to aneurysm clip.

Discussion

Our hypothesis is that this patient was misdiagnosed with stroke and that the post-thrombolysis bleeding area could represent an intratumoral hemorrhage.

The rates of MIM treated with IVtPA range from 1.4 to 16.7%[1,3] A recent multicenter study[3] suggests that thrombolysis in stroke mimics is safe because the rate of symptomatic intracranial hemorrhage (SICH) was low, and death was not attributed to the bleeding. The SICH rate in MIM was 1.0%, compared with 7.9% in strokes.[3]

A case of hemorrhage after thrombolysis for a presumed stroke in a patient with glioblastoma was previously reported.[4] As in our case, bleeding did not lead to worsening of the clinical outcome.[4] Despite this, some authors[2,5] suggest that t-PA in patients with GBM could degenerate the extracellular matrix, facilitating tumor spread.

Conclusion

Brain tumors should be considered in the differential diagnosis of acute ischemic events. The present case report highlights the challenges of interpreting the initial CT, recognizing MIM, and the risk of IV-TPA in nonstroke conditions, which, according to the current literature, does not exceed the benefits of thrombolytic therapy.

Conflict of Interests

The authors have no conflict of interest to declare.

References

1 Nguyen PL, Chang JJ. STROKE MIMICS AND ACUTE STROKE EVALUATION: CLINICAL DIFFERENTIATION AND COMPLICATIONS AFTER INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR. J Emerg Med 2015;49(02):244–252. Doi: 10.1016/j.jemermed.2014.12.072

2 Klüenemann HH, Skljarevski V, Hamill RW. A stroke-like presentation of glioblastoma multiforme. J Stroke Cerebrovasc Dis 2003; 12(01):47–48. Doi: 10.1053/jscd.2003.8

3 Zinkstok SM, Engelter ST, Gensicke H, et al. Safety of thrombolysis in stroke mimics: results from a multicenter cohort study. Stroke 2013;44(04):1080–1084. Doi: 10.1161/STROKEAHA.111.000126

4 Grimm SA, DeAngelis LM. Intratumoral hemorrhage after thrombolysis in a patient with glioblastoma multiforme. Neurology 2007; 69(09):936–936. Doi: 10.1212/01.wnl.0000265392.03231.ac

5 Chen H, Cebula H, Schott R, Dietemann JL, Froelich S. Glioblastoma multiforme presenting with ischemic stroke: case report and review of the literature. J Neuroradiol 2011;38(05):304–307. Doi: 10.1016/j.neurad.2011.01.008

Cerebral Venous Sinus Stenting for the Treatment of Idiopathic Intracranial Hypertension in a Child

Angioplastia de Seio Venoso Cerebral para Tratamento de Hipertensão Intracraniana Idiopática em Criança

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Abstract

Idiopathic intracranial hypertension (IIH) is a disease characterized by an increase in the opening pressure of the cerebrospinal fluid (CSF) associated with symptoms of elevated intracranial pressure (ICP). The condition is more prevalent in women and typically managed clinically. Surgical treatment is reserved for select refractory cases. The well-established surgical procedures for the management of IIH are CSF shunting and fenestration of the optic nerve sheath. These procedures, however, are associated with high rates of complication and recurrence.

More recently, venous sinus angioplasty with stents has been employed in cases with documented narrowing of the sigmoid-transverse sinuses. This technique is associated with a significant reduction in the venous pressure gradient at the stenosis site, alleviating the symptoms of intracranial hypertension.

We report a case of a previously healthy 12-year-old patient who presented with 10-day history of headaches, blurring of vision, nausea and vomiting, which evolved with worsening of the visual acuity and papilledema. Imaging scans disclosed stenosis of the right transverse and sigmoid sinuses. The patient underwent stenting of the stenotic venous segments and showed good evolution, with significant clinical improvement within 24 hours of the procedure.

Keywords

- intracranial hypertension
- papilledema
- pseudotumor cerebri
- intracranial thrombosis
- endovascular procedures

Resumo

A hipertensão intracraniana idiopática (HII) é uma doença caracterizada pelo aumento da pressão de abertura do líquido cefalorraquidiano associado a sintomas de aumento da pressão intracraniana. É mais frequente em mulheres, sendo habitualmente tratada

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com medidas clínicas. O tratamento cirúrgico é reservado a uma minoria de casos que se mostram refratários. Os procedimentos cirúrgicos consagrados para este fim são a derivação liquórica e a fenestração de bainha do nervo óptico. Entretanto, eles estão associados a altos índices de complicações e recorrência.

Mais recentemente, a angioplastia de seio venoso com uso do *stent* vem sendo utilizada em casos em que há redução documentada no calibre dos seios transverso-sigmoide com repercussão comprovada no gradiente pressórico. Essa técnica está associada a uma redução significativa no gradiente de pressão venosa no local da estenose. Consequentemente, resulta em alívio dos sintomas da hipertensão intracraniana.

Neste trabalho, descrevemos o caso de um paciente de 12 anos de idade, sem doenças prévias, que apresentava quadro de cefaleia, turvação visual, náuseas e vômitos de início havia dez dias, tendo evoluído com piora da acuidade visual e papiledema. Realizou exame de imagem que identificou estenose dos seios transversos e sigmoide à direita. O paciente foi submetido a angioplastia dos segmentos venosos estenosados, apresentando boa evolução, com melhora clínica significativa já nas primeiras 24 horas após o procedimento.

Palavras-chave
- hipertensão intracraniana
- papiledema
- pseudotumor cerebral
- trombose intracraniana
- procedimentos endovasculares

Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a syndrome with unknown etiology characterized by documented high opening pressure of the cerebrospinal fluid (CSF) on lumbar puncture (initial pressure $>$ 25 cm H2O).[1] The condition is associated with increased intracranial pressure (ICP), no localizing focal neurological signs (with exception of abducens nerve palsy), together with neuroimaging disclosing no cerebral abnormalities or hydrocephaly.[1]

The physiopathology of IIH is not fully understood, and a number of mechanisms have been proposed to explain the condition, ranging from increased CSF production/reduced CSF absorption, to increased cerebral venous pressure.[2] It has been acknowledged that patients with IIH often present unilateral or bilateral stenosis of the transverse sinus.[3] Despite controversy over whether transverse sinus stenosis plays a role in the physiopathology of IIH, angioplasty of the transverse sinus by stent placement can lower pre- and poststenosis gradient pressure, reduce venous and intracranial pressures by improving CSF reabsorption, and promote an improvement in symptoms.

In the present study, we report the case of a pediatric patient with IIH who underwent venous sinus stenting with subsequent improvement in symptoms. We also discuss the main aspects of this condition, based on a review of the literature.

Case Report

A previously healthy 12-year-old male patient presented with a 10-day history of headache together with blurred vision, dizziness, nausea and vomiting. The patient's condition declined, with worsening visual acuity, in the three days leading up to admission to the Emergency Room. A consultation with the ophthalmologist resulted in a diagnosis of papilledema on an ocular fundus exam.

Computed tomography (CT) and magnetic resonance imaging (MRI) scans of the head with arterial and venous angiography (►**Fig. 1**) revealed signs of intracranial hypertension and narrowing at the transition of the transverse/sigmoid sinuses bilaterally. Given the suspected case of IIH associated with bilateral stenosis of the venous sinuses, cerebral angiography with microcatheter placement was performed to measure the pressure gradient and determine the need for angioplasty.

Endovascular Procedure

The night prior to the procedure, clopidogrel 300 mg and acetylsalicylic acid (ASA) 200 mg were administered. The procedure commenced with puncture of the left femoral artery and right common femoral vein with introduction of a 4F sheath using the Seldinger technique. A 4F vertebral diagnostic catheter was advanced via the left for the cerebral angiography study, which revealed severe stenosis of around 80% to 85% at the transition of the sigmoid-transverse sinuses bilaterally (►**Fig. 2A**). The study also showed redirecting of the supratentorial venous drainage to the diploic veins, and from the scalp in the frontoparietal convexity bilaterally.

A Head-Hunter (Merit Medical OEM, Salt Lake City, UT, US) 4F catheter was then advanced via the femoral vein, positioned at the right internal jugular vein, and, using coaxial catheter placement, an Excelsior (Stryker Neurovascular, Fremont, CA, US) SL10 microcatheter was advanced with the aid of a Transend Platinum (Stryker Neurovascular) microguide. Manometry of the intracranial venous sinuses was then performed, disclosing pre- and poststenosis pressure gradients, as described in ►**Table 1**.

Angioplasty with right stent placement was performed, because the left sinuses exhibited hypoplasia. The jugular-

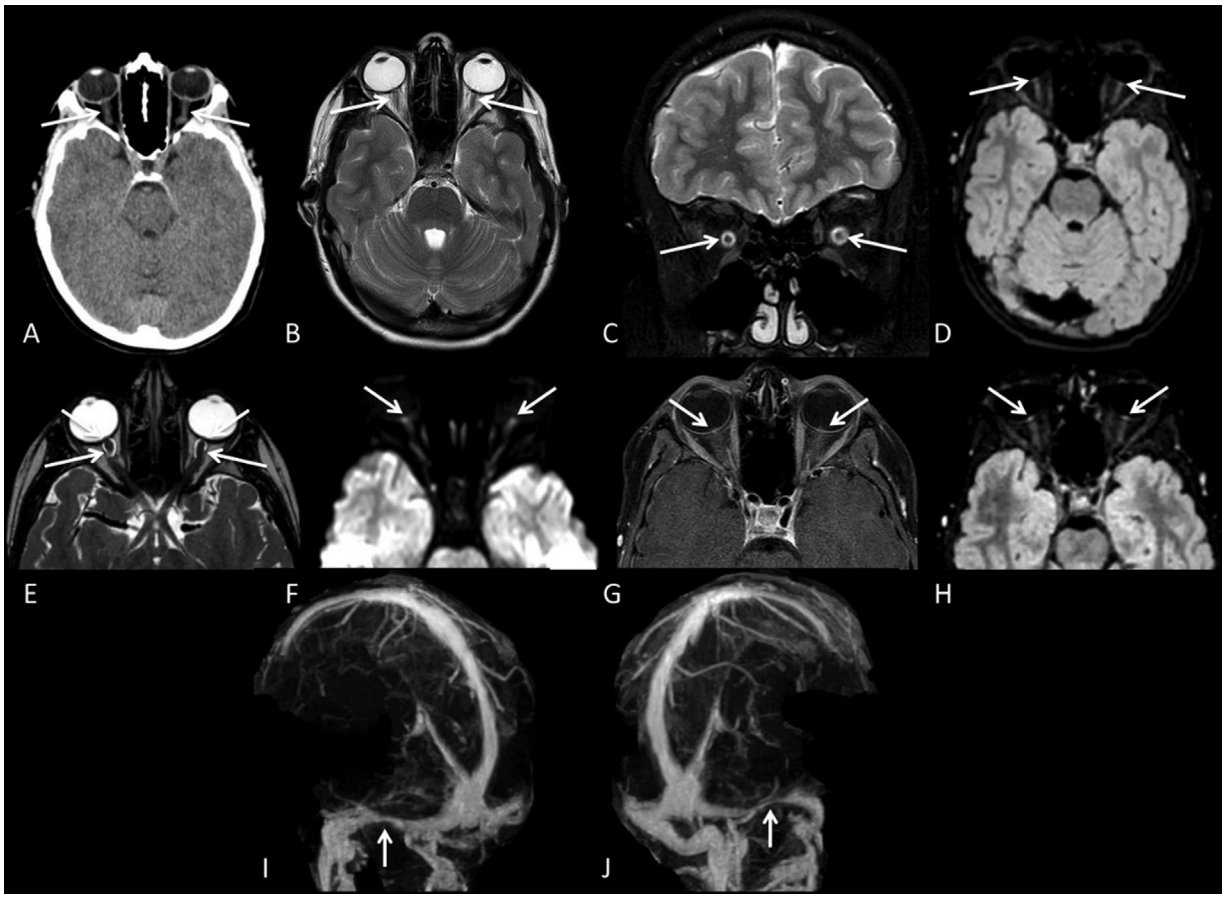

Fig. 1 (**A**) Computed tomography (CT) without contrast revealing cerebrospinal fluid (CSF) distension of the optic nerve sheath (white arrows). (**B**,**C**) T2-weighted axial and coronal sequences again showing CSF distension of the optic nerve sheath (white arrows). (**D**) Fluid-attenuated inversion recovery (FLAIR) weighted axial sequence revealing hyperintensity of the optic papilla (red arrows). (**E**,**F**,**G**,**H**) T2 driven equilibrium (DRIVE), diffusion-weighted imaging (DWI), T1 postcontrast and FLAIR postcontrast sequences to assess orbits provide a clearer view of the CSF sheath distension (blue arrows) and signs of bilateral papilledema (red arrows), displaying hyperintensity in diffusion sequence, postcontrast intensity on T1 and FLAIR, with the latter providing greater sensitivity. (**I**,**J**) Magnetic resonance angiography showing bilateral stenosis at the transition between the transverse and sigmoid sinuses (green arrows).

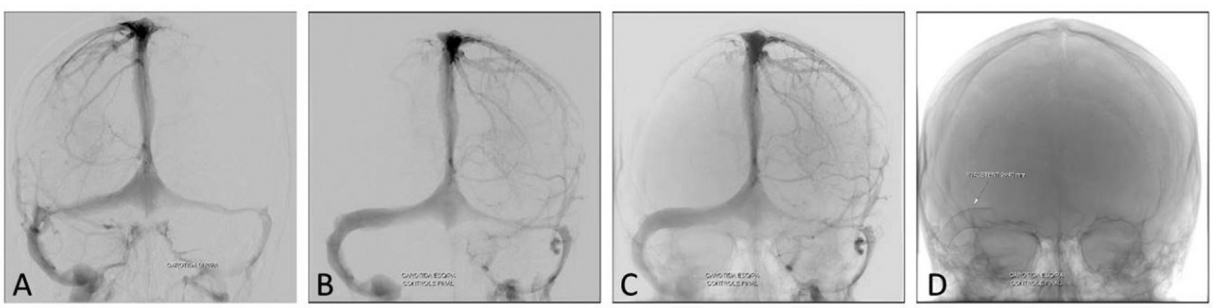

Fig. 2 (**A-C**) Front carotid angiogram disclosing: (**A**) bilateral stenosis at the transition of the transverse and sigmoid sinuses; (**B**,**C**) after venous angioplasty of the right transverse and sigmoid sinuses, with restoration of the normal caliber; (**D**) final position of the stent at the topography of the transition between the right transverse and sigmoid sinuses. **A** and **B**: with bone subtraction; **C** and **D**: without bone subtraction.

vein catheter was removed, and the short 4F sheath was replaced by a long NeuroMax (Penumbra, Inc., Alameda, CA, US) 8F sheath. With the aid of a Neuron Select (Penumbra, Inc.) 6F catheter and hydrophilic 0.035" stiff guidewire, the NeuroMax (Penumbra, Inc.) 8F sheath was advanced up to the right transverse sinus beyond the stenosis site. A 9×40 mm Carotid Wallstent (Boston Scientific Corporation, Marlborough, MA, US) was then advanced and deployed to cover the transition of the right sigmoid-transverse sinuses (►**Fig. 2**). An *Excelsior* (Stryker Neurovascular) SL10 microcatheter was then advanced with the aid of a *Transend Platinum* (Stryker Neurovascular) microguide, and manometry of the intracranial venous sinuses was performed (data shown in ►**Table 1**).

The endovascular procedure was performed under general anesthesia and systemic heparinization. In the first 24 hours

Table 1 Values obtained by intracranial sinus manometry, before and after angioplasty

SITE	PREANGIOPLASTY MANOMETRY	POSTANGIOPLASTY MANOMETRY
Right internal jugular vein	10 mmHg	9 mmHg
Left internal jugular vein	10 mmHg	10 mmHg
Right sigmoid sinus	11 mmHg	10 mmHg
Left sigmoid sinus	11 mmHg	10 mmHg
Right transverse sinus	22 mmHg	10 mmHg
Left transverse sinus	22 mmHg	11 mmHg
Torcula	23 mmHg	11 mmHg

after the procedure, the patient reported an improvement in the headache. The blurring of vision gradually improved over the ensuing days. The patient was discharged from hospital on the third postoperative day, and was prescribed clopidogrel 75 mg/day for 3 months and ASA 100 mg/day for 1 year. A 3-month follow-up MRI confirmed improvement in the signs of intracranial hypertension (►**Fig. 3**).

Discussion

The annual incidence of IIH is of approximately 1 case for every 100,000 people, reaching up to 20 cases per 100,000 people when the population is constrained to obese women aged between 20 and 44 years.[4,5]

For many years, IIH was interpreted as "intracranial hypertension secondary to arterial hypertension", and regarded as a manifestation of brain edema due to a variety of different pathologies, including obstructive sleep apnea, chronic kidney disease, or connective tissue disorders.[6] Another theory involves impairment of CSF absorption due to overuse of vitamin A derivatives, antibiotics, and hormonal contraceptives.[7] Other studies highlight the importance of obesity in compromising intracranial venous drainage as a result of elevated intra-abdominal and right atrial venous pressures. These increases in pressure hamper cerebral venous return flow, increasing cerebral venous pressure.[8]

Unlike the cases typically found in the literature, in which around 86% of the patients with IIH are adult females with an average body mass index (BMI) $> 30\ kg/m^2$,[9] the case herein reported is of a boy with normal BMI. However, recent recommendations do not support the use of BMI as a predictive factor for venous sinus stenosis.[10] Thus, BMI should not be employed as a criteria to select patients for complementary investigations using angiography by catheter.

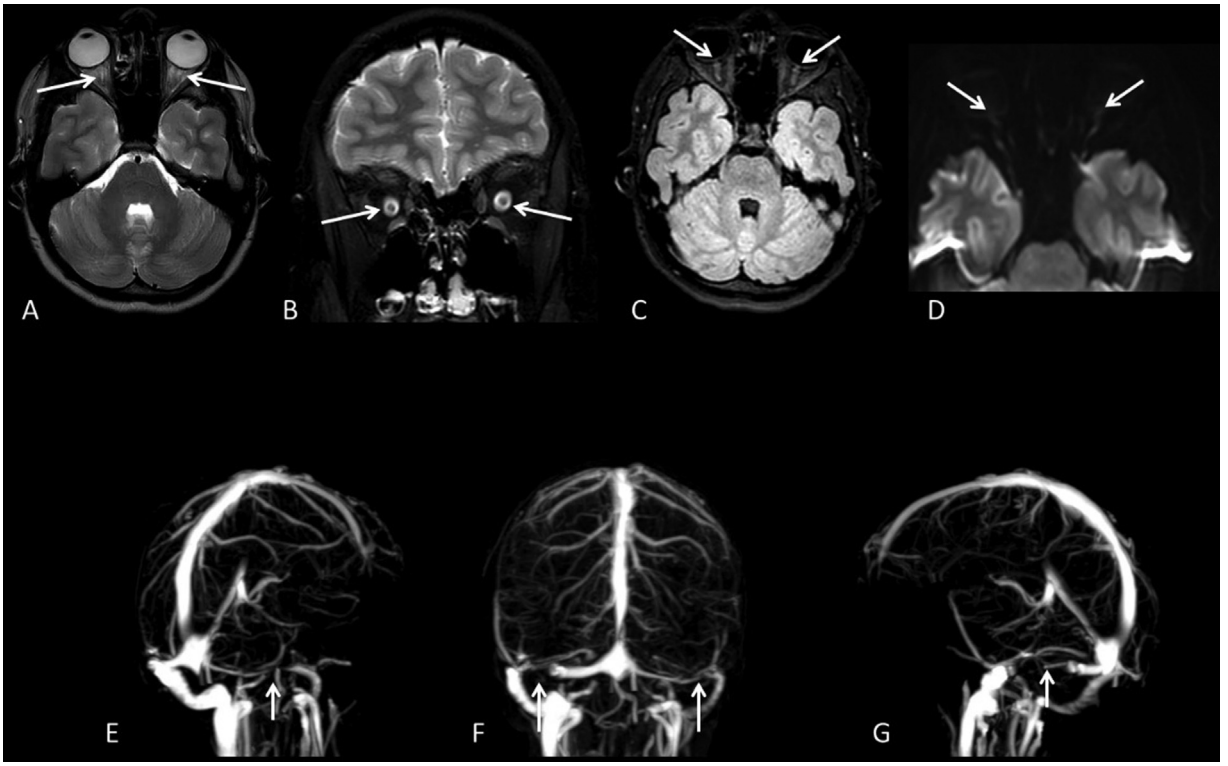

Fig. 3 (**A**,**B**): T2-weighted axial and coronal sequences showing distension of the optic nerve sheath, which was stable relative to a previous study. (**C**,**D**) FLAIR and DWI-weighted axial sequence revealing slight protrusion of the optic papilla, characterized by a slight hypersignal on the FLAIR sequence (white arrows), lower than that of the previous study, but not exhibiting hypersignal on the diffusion sequence (white arrows). (**E**,**F**,**G**) Magnetic resonance angiography showing stenosis at the transition between the left transverse and sigmoid sinuses (white arrows), stable relative to that of the previous study, highlighting material characterizing artefact with magnetic susceptibility contralaterally consistent with the stent (white arrow).

In IIH patients, MRI studies reveal empty sella turcica, cerebellar tonsillar herniation, meningoceles, CSF fistula, and venous stenoses of the sigmoid-transverse sinuses.[11] In the case herein reported, the patient presented distension of the optic nerve sheath and hyperintensity of the optic papilla. The main goals of the treatment include reducing the ICP to alleviate the symptoms of headache and preserve vision.[11] Persistent papilledema can develop with progressive optic atrophy, visual disability, and blindness.

The classic approaches for the management reported in the literature include weight loss, treatment using a carbonic anhydrase inhibitor (acetazolamide), and serial lumbar taps, traditionally considered auxiliary measures in the treatment of select cases.[12,13] Patients with refractory IIH can be treated by fenestration of the optic nerve sheath or CSF shunts (ventriculoperitoneal or lumboperitoneal CSF shunting). These procedures, however, are associated with high rates of complication and recurrence.[12]

Recently, impaired venous drainage systems due to bilateral focal stenosis of cerebral venous sinuses (generally at the transverse-sigmoid transition) have become the focus of attention as a possible cause of IIH. Bilateral stenosis of venous sinuses is commonly associated with the occurrence of IIH, found in more than 50% of the patients. Most of these cases fail to respond to initial the weight-loss and acetazolamide therapy. The rates can reach 100% among patients refractory to the initial procedures.[11,13,14] Whether venous stenosis is a cause or consequence of IIH remains unclear, but studies[11,13] show that reducing cerebral venous pressure by implanting stents within the narrow venous segment is an effective approach to resolve the signs and symptoms of IIH.

In fact, decreasing the intraluminal pressure of the venous system promotes greater CSF absorption in the arachnoid granulations, in turn reducing the ICP.[11,14] This notion was confirmed by Ding et al.[15] in 2014, who showed a reduction in ICP after venous sinus stenting in a patient with IIH. Akin to the case herein reported, most previous studies[4,11,16] show pre- and poststenosis sinus pressure gradients. Some reports[4,11,16] demonstrate the importance of a pressure gradient $\geq$ 8 mmHg as a criteria for an indication of sinus stenting – as applied in the case herein presented. Patients with a pressure gradient between 4 mmHg and 7 mmHg can show some benefit from stenting in specific cases.[4,11,16]

Stenosis of the transverse/sigmoid sinus can be classified into two types: intrinsic discrete stenosis, with clearly demarcated intraluminal narrowing, secondary to arachnoid granulations, fibrous septa. or fat deposits; and long stenosis narrowing with normal arachnoid granulations on imaging, secondary to extrinsic compression from swollen brain parenchyma.[16] Patients with IIH generally present the latter pattern of transverse/sigmoid sinus stenosis, the same pattern seen in the case reported in the current study.[16]

This stenosis causes a slowing of venous outflow, resulting in venous hypertension. Consequently, CSF reabsorption is decreased, and ICP is further increased. External compression of the sinus then increases, with progressive collapse of its walls and further stenosis, exacerbating venous and intracranial hypertension via a feedback mechanism.[4,13]

The use of venous stents is associated with a significant reduction in venous pressure gradient across the stenosis site before and after the procedure, as evidenced in the case herein presented (►**Table 1**). Consequently, stent deployment can interrupt the feedback mechanism described and result in relief of the IIH symptoms.[17]

Currently, there is no evidence suggesting that one type of stenting is superior to another to treat venous sinus stenosis. Similarly, the benefits of bilateral versus unilateral stent implantation in transverse sinuses remain unclear. In the present case, unilateral venous stent implant was performed in the dominant transverse/sigmoid segment only.[18]

Adjuvant antiplatelet therapy can be administered before stent implantation and maintained for 3 to 6 months, although there is no consensus on the optimal length of treatment.[11,18,19] No data are available to support the inferiority of single versus dual antiplatelet therapy, but thromboembolic complications have been reported with the use of aspirin alone.[17]

Some complications with the technique have been reported (venous sinus perforation, stent migration, intraprocedural stent thrombosis, subdural hemorrhage, and development of further stenoses immediately proximal or distal to the stent), although no complications were observed in the case herein presented.[12,13]

Conclusion

Venous sinus stent implantation is increasingly used for the management of IIH in the presence of bilateral stenosis of the cranial sinuses. Stent implantation can widen the narrowed sinus and facilitate venous drainage, thereby reducing intracranial hypertension. Although long-term follow-up is necessary, several studies show that stent placement for the management of symptomatic stenoses of transverse-sigmoid sinuses may be a safe and durable treatment that provides symptom relief in IIH patients.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002;59(10):1492–1495
2 McGeeney BE, Friedman DI. Pseudotumor cerebri pathophysiology. Headache 2014;54(03):445–458
3 Elder BD, Goodwin CR, Kosztowski TA, et al. Venous sinus stenting is a valuable treatment for fulminant idiopathic intracranial hypertension. J Clin Neurosci 2015;22(04):685–689
4 Dinkin MJ, Patsalides A. Venous sinus stenting in idiopathic intracranial hypertension : results of a prospective trial. J Neuroophthalmol 2017;37(02):113–121
5 Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. Arch Neurol 1988;45(08):875–877
6 Acheson JF. Idiopathic intracranial hypertension and visual function. Br Med Bull 2006;79-80:233–244
7 Warner JEA, Larson AJ, Bhosale P, et al. Retinol-binding protein and retinol analysis in cerebrospinal fluid and serum of patients with and without idiopathic intracranial hypertension. J Neuroophthalmol 2007;27(04):258–262

8 Binder DK, Horton JC, Lawton MT, McDermott MW. Idiopathic intracranial hypertension. Neurosurgery 2004;54(03):538–551, discussion 551–552
9 Galgano MA, Deshaies EM. An update on the management of pseudotumor cerebri. Clin Neurol Neurosurg 2013;115(03): 252–259
10 Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ. O'Reilly MW, Sinclair AJ. Metabolic concepts in idiopathic intracranial hypertension and their potential for therapeutic intervention. J Neuroophthalmol 2018;38(04):522–530
11 Al-Mufti F, Dodson V, Amuluru K, et al. Neuroendovascular cerebral sinus stenting in idiopathic intracranial hypertension. Intervent Neurol 2020;8(2-6):164–171
12 Satti SR, Leishangthem L, Chaudry MI. Meta-Analysis of CSF diversion procedures and dural venous sinus stenting in the setting of medically refractory idiopathic intracranial hypertension. AJNR Am J Neuroradiol 2015;36(10):1899–1904
13 Daggubati LC, Liu KC. Intracranial venous sinus stenting: a review of idiopathic intracranial hypertension and expanding indications. Cureus 2019;11(02):e4008
14 Gurney SP, Ramalingam S, Thomas A, Sinclair AJ, Mollan SP. Exploring the current management idiopathic intracranial hypertension, and understanding the role of dural venous sinus stenting. Eye Brain 2020;12:1–13
15 Ding D, Starke RM, Durst CR, Crowley RW, Liu KC. Venous stenting with concurrent intracranial pressure monitoring for the treatment of pseudotumor cerebri. Neurosurg Focus 2014;37(1, Suppl):1
16 Miyachi S, Hiramatsu R, Ohnishi H, Takahashi K, Kuroiwa T. Endovascular treatment of idiopathic intracranial hypertension with stenting of the transverse sinus stenosis. Neurointervention 2018;13(02):138–143
17 Giridharan N, Patel SK, Ojugbeli A, et al. Understanding the complex pathophysiology of idiopathic intracranial hypertension and the evolving role of venous sinus stenting: a comprehensive review of the literature. Neurosurg Focus 2018;45(01): E10
18 Saber H, Lewis W, Sadeghi M, Rajah G, Narayanan S. Stent survival and stent-adjacent stenosis rates following venous sinus stenting for idiopathic intracranial hypertension: a systematic review and meta-analysis. Intervent Neurol 2018;7(06):490–500
19 Silva JMA, Conti MLM, Aguiar GB, et al. Endovascular treatment for idiopathic intracranial hypertension improves clinical symptoms and signs. Arq Bras Neurocir 2017;36:1–6

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Peerless SJ, Hernesniemi JA, Drake CG. Surgical management of terminal basilar and posterior cerebral artery aneurysms. In: Schmideck HH, Sweet WH, editors. Operative neurosurgical techniques. 3rd ed. Philadelphia: WB Saunders; 1995:1071–86.

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Theses and dissertations

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