

Headache associated with pituitary tumors

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Abstract The objective of this study is to analyze the presence of headache in pituitary tumors and their characteristics, the relationship between pituitary tumor size, biological type, local extension and intrasellar pressure (ISP). This is a prospective study, of 64 consecutive patients presenting with primary pituitary masses at Neuroendocrinological Department of General Hospital of Fortaleza from October 2005 to December 2006. We analyzed sex, age, headache (laterality, site, severity, quality, frequency, duration, associated symptoms, time of onset, trigger, alleviating factors and familial history) and tumor characteristics (type, size, quiasmatic compression, cavernous sinus invasion, sella turcica destruction, cystic or solid mass and ISP). We observed a statistic significant factor between pituitary tumor and tumor size, optic compression, sellar destruction, cavernous sinus invasion and ISP. Biochemical-neuroendocrine factors, mainly in prolactinomas, seem to be an important factor in the determination of headache. The presence of headache in pituitary tumor is related to a combination of factors, including ISP, tumor extension, relationship with the sellar structures, patient predisposition, familial history, and functional disturbance within the hypothalamo-pituitary axis.

Keywords Headache · Intrasellar pressure · Pituitary adenoma

Introduction

Pituitary adenomas are basal midline tumors in the sella region, which are associated with headache in some patients. The reported incidence of headache associated to pituitary adenomas varies from 33 to 72% [1, 2]. It has long been considered that headache is related to tumor size and dural traction on the pain-sensitive structures in this area [1, 3]. The explanation for dural traction as a cause of headache is that the expansion of a pituitary tumor within the sella turcica stimulates afferent fibers innervating the dura mater, which are certainly known to be pain producing [4].

Invasion of the cavernous sinus by tumors has also been invoked to explain headache [5] since the sinus contains the ophthalmic branch of the trigeminal nerve and the internal carotid artery, both of which could generate head pain.

Some authors suggest that tumor activity may be important in some forms of pituitary tumor associated headache [7, 8], mainly because of the presence of headache in small tumors [5, 7]. The fact that headache can be dramatically improved or worsened by endocrine treatments [8], in the absence of any measurable change in pituitary size, suggests that pituitary tumor associated headache may also have a biochemical-neuroendocrine origin [6]. The headache can also have a relation with the intra sellar pressure [9].

The objectives of this study are to analyze the associations between pituitary tumor size, biologic type of tumor, local extension of the tumor, ISP and headache characteristics.

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Methods

Study design

In this prospective designed study, we describe 64 consecutive patients presenting with primary pituitary masses at Neuroendocrinological Department of General Hospital of Fortaleza from October 2005 to December 2006. We analyzed sex, age, headache (laterality, site, severity, quality, frequency, duration, associated symptoms, time of onset, trigger, alleviating factors and familial history) and tumor characteristics (type, size, quiasmatic compression, cavernous sinus invasion, sella turcica destruction, cystic or solid mass and ISP).

The characteristics of headache were collected by a questionnaire, which was administered by one of the authors.

All patients underwent ophthalmologic and endocrinology examinations. Cavernous sinus invasion, optic chiasm compression and pituitary apoplexy were analyzed by MRI study of all patients.

Endocrinological assessment

The endocrinological investigation was performed in our hospital. Multiple measurements of plasma GH, insulin-like growth factor-I (IGF-I), prolactin, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were studied.

Neuroradiology

All patients underwent tumor evaluation with magnetic resonance imaging (MRI), with and without administration of intravenous contrast agent. We utilized a 1.5 Tesla MRI with coronal and sagittal *T1* and *T2*-weighed spin echo before and after gadolinium-base contrast medium. Tumor size was classified according to maximum tumor diameter into two categories: microadenoma (<10 mm), and macroadenomas (≥ 10 mm). Chiasm compression, cavernous sinus invasion and sella turcica destruction were diagnosed on the basis of radiological appearance and considered present or absent, using standard radiological criteria [12].

Tumor volume

For assessment of tumor volume, we used the Cavalieri's principle, assuming that pituitary tumors are considered as an ellipsoid [10, 11]. We calculated the volume using the following equation: volume = $[4/3 \pi(a/2 \cdot b/2 \cdot c/2)]$. In cases of large and multilobed tumor, the volume was assumed to consist of separate ellipses and the sum of each lobe volume was calculated.

Statistical analysis

All data are expressed as mean \pm standard deviation (SD). Pearson rank correlation, *T* tests and Fisher's exact test were used for analysis of statistical significance, with $P < 0.05$ considered significant. Statistical software, SPSS 16.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

Results

Patients characteristics

Of the 64 patients interviewed, 36 were female (56.2%); the mean age was 42.08 ± 16.49 years. The most common types of tumor presented in the study were nonfunctioning adenomas, representing 46.9% ($n = 30$), followed by prolactinomas, 18.8% ($n = 12$) and ACTH producing adenomas, 17.2% ($n = 11$) (Table 1).

Headache characteristics

Headache was a major complaint for 44 patients (68.8%) in our study group. There was no difference in headache incidence according to gender ($P = 0.89$). Fourteen patients (31.8%) who reported to present headache (44 patients) had a positive familial history of chronic headache. Four patients with no pain complaint also reported a positive headache history in family. There was no association between familial history and presence of headache in our study group ($P = 0.384$, Fisher's exact test).

Site and laterality

The headache affected the frontal region in most of those patients (61.36%, $n = 27$), followed by the orbital (22.7%, $n = 10$) and retrorbital regions (15.9%, $n = 7$). Bilateral headache was present in 59% of patients ($n = 26$).

Severity

Most of the patients reported to present severe headache (34%, $n = 15$). Mild, moderate, and excruciating headache were reported in 15.9% ($n = 7$), 31.8% ($n = 14$) and 18.2% ($n = 8$), respectively.

Quality

Throbbing was the most common classification of pain quality (54.5%, $n = 24$) followed by dull (15.9%, $n = 7$), pressure (15.9%, $n = 7$), sharp (11.3%, $n = 5$), and burning (2.2%, $n = 1$).

Table 1 Patients characteristics

Tumor type <i>n</i> (%)	Micro <i>n</i> (%)	Macro <i>n</i> (%)	QC <i>n</i> (%)	CSI <i>n</i> (%)	SD <i>n</i> (%)	Headache <i>n</i> (%)
NFA 30 (46.9)	0 (0)	30 (100)	27 (90)	15 (50)	19 (63)	23 (77)
Prolactinoma 12 (18.8)	1 (8)	11 (92)	7 (58)	6 (50)	5 (42)	10 (83)
Cushing's 11 (17.2)	9 (82)	2 (18)	2 (18)	2 (18)	2 (18)	5 (45)
Acromegaly 8 (12.5)	2 (25)	6 (75)	1 (12)	1 (12)	2 (25)	3 (37)
Craniofaringioma 3 (4.7)	0 (0)	3 (100)	3 (100)	0 (0)	1 (33)	3 (100)
Total 64 (100)	12 (19)	52 (81)	40 (62)	24 (37)	29 (45)	44 (69)

NFA nonfunctioning adenoma, Micro microadenoma, Macro macroadenoma, QC quiasmatic compression, CSI cavernous sinus invasion, SD sella destruction

Table 2 Duration, frequency and associated symptoms of headache

Characteristics	Patients <i>n</i> (%)
Frequency	
<1×/week	5 (11.4)
1×/week	5 (11.4)
2–3×/week	6 (13.6)
>3×/week	5 (11.4)
>15 days/month	23 (52.3)
Associated symptoms	
Photophobia	22 (50)
Nausea	20 (45.4)
Restlessness	12 (27.2)
Vomiting	7 (15.9)
Osmophobia	7 (15.9)
Aggravation with movement	7 (15.9)
Ophtalmoplegia	1 (2.2)

Duration and frequency

The majority of patients with headache presented the complaint for at least 1 year (72.7%, *n* = 32). Only eight patients presented it for more than 12 months. The mean duration of pain attacks were 478.86 ± 633.15 min. Using the definition of chronic daily headache as 15 headache days or more per month [12, 13], the frequency of chronic daily headache was 52.3% (*n* = 23) (Table 2).

Associated symptoms, alleviating factors and triggers

The non-pharmacological alleviating factors included rest (61.3%), fresh bath (29.5%) and caffeine ingestion (9%). Trigger factors that were recorded were physical activity (25%), stress (22.7%) and hunger situation (Table 3).

Table 3 Associated symptoms, alleviating factors and triggers

Characteristics	Patients <i>n</i> (%)
Alleviating factors	
Rest	27 (61.3)
Bath	13 (29.5)
Caffeine ingestion	4 (9)
Fresh air	1 (2.2)
Triggers	
Physical activity	11 (25)
Stress	10 (22.7)
Hunger	3 (6.8)
Smoking	1 (2.2)

Tumor characteristics

Tumor size (Table 1)

The mean tumor size presented in our study group was 26.93 ± 14.59 mm. Microadenomas and macroadenomas represented, respectively, 18.75% (*n* = 12) and 81.25% (*n* = 52) of the cases. Nonsecreting tumors were larger than functioning adenomas (28.7 ± 10.18 mm × 20.29 ± 18.32 mm, *P* < 0.05).

Macroadenomas (≥10 mm) presented a higher incidence of headache (*P* = 0.026, Pearson Chi-square test).

Type of tumor

Nonfunctioning tumors and secreting adenomas represented, respectively, 51.5% (*n* = 33) and 48.4% (*n* = 31) of the sellar lesions presented. There was no statistical difference between those groups about association to headache (*P* = 0.106, Fisher's exact test). In the group of

pituitary adenomas (Table 1), prolactinomas presented the highest headache incidence (83%).

Solid and cystic lesions

Predominantly solid lesions were present in 59.3% ($n = 38$). Cystic components were present in 40.6% ($n = 26$) of the patients. There was no statistical difference between solid and cystic lesions in relation to headache occurrence ($P = 0.7$).

Optic chiasm compression and sellar destruction

The occurrence of compression of the chiasm was associated to the presence of headache ($P = 0.004$, Fisher's exact test). Large tumors, which caused sellar erosion, were also associated to headache ($P = 0.28$, Fisher's exact test).

Cavernous sinus invasion

The presence of unilateral or bilateral invasion of cavernous sinus was positively associated to occurrence of headache ($P = 0.014$, Fisher's exact test).

Discussion

In population-based surveys, headache occurs in approximately 4–5% of the general population (US 4.1%, Greece 4.4% and Spain 4.7%) [14–16]. The overall prevalence of headache in brain tumor is about 60% and the sole symptom is only 2% [17]. The incidence of headache among patients with pituitary adenoma has been reported to be 33 to 72% [17]. Patients with pituitary tumors present a higher incidence of headache. In our study group the headache was present in 69%, with no significant difference between genders. Levy et al. [18] has found the same results with a reported 70% of headache incidence in patients with pituitary lesions, suggesting participation of pituitary tumors in origin of headache.

In our study group the finding of a family history of headache do not suggests a higher predisposing to the primary headache than the general population [14]. Fourteen patients (31.8%) who reported to present headache (44 patients) had a positive familial history of chronic headache, and four patients (20%) with no pain complaint (20 patients) also reported a positive headache history in the family. There was no association between familial history and presence of headache in our study group ($P = 0.384$, Fisher's exact test). In the contrary of Levy et al. [18], that found a strong connection between pituitary-associated headache and a family history of headache.

The clinical characteristics of headache in pituitary tumor are extremely variable. Most patients present a phenotype that mapped well onto International Headache Society (IHS) [12, 13] primary headache diagnoses: chronic migraine [19], episodic migraine, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), cluster headache [20], hemicrania continua and isolated primary stabbing headache [21].

Headache from brain tumor is generally related to traction and displacement of intracranial pain-sensitive structures located in the blood vessels, cranial nerves and dura mater. Some other conditions associated to development of headache are: inflammation involving pain-sensitive structures, meningeal irritation or its involvement in spreading tumors, and psychological and biochemical causes [28]. The cavernous sinus contains pain-producing structures, such as the internal carotid artery and trigeminal nerve and ganglion, invasion of which might be expected to cause pain. In this series the presence of unilateral or bilateral invasion of cavernous sinus were associated to the occurrence of headache. In the series of Levy [11] and Abe [17] the cavernous sinus invasion does not appear to be predictive of headache in pituitary tumors per se.

The clinical picture of pituitary tumors is characterized by two levels of symptoms: (1) focal symptoms related to tumor location, such as cavernous sinus invasion, chiasm compression, ISP, sellar destruction, and (2) endocrinological disturbance. Recently, the hypothesis of a biochemical-neuroendocrine participation in the pituitary tumor headache genesis has been strongly suggested. The use of somatostatin analogs, such as octreotide, in acromegaly patients with associated headache is related to immediate analgesic effect in some of them [8, 22]. Similar phenomenon occurs with dopamine-agonists in patients with prolactinomas [23–25]. However, significant exacerbation of the headache has also been reported when these drugs are used [26].

Neuroendocrinological signaling alterations probably contribute to initiation of headache and represent an important variable in the determination of the severity of symptoms. Some authors describe an important predisposition of headache in patients with acromegaly and prolactinoma, suggesting that these functional tumors are particularly pronociceptive [8, 22]. We observed higher prevalence of headache in patient with prolactinomas, when compared to others functioning pituitary adenomas, but we did not observed the same with GH producing tumors. Patients with corticotrophin producing adenoma (Cushing disease) had a headache incidence of 45%. Dopamine–prolactin axis seems to play an important role in development of migraine and, apparently also has a

major importance in headache secondary to prolactinomas (25m29).

Although previous series [11, 13] did not find relation between headache and pituitary tumor volume, nor with cavernous sinus invasion, in our study we observed a statistical association between headache presence and tumor size, optic chiasm compression, sellar destruction and cavernous sinus invasion, suggesting an association between extension of the lesion and severity of symptoms, probably by the great number of macroadenoma (81.2%) and a high mean tumor size, 24.6 ± 15.1 mm. We believe that dural stretch and local cavernous sinus invasion are important mechanisms in the origin of pituitary tumor associated headache. It seems that lesions of the anatomical structures studied have an important role as trigger factors for pituitary tumor related headache.

We can speculate that the genesis of headache in patients with pituitary tumor can be due to the intra sellar pressure [27, 28]. The growth of a tumor into the sella turcica will increase the ISP progressively and then the compression of the diaphragm and sellar dura. If the tumor destroys the sellar region, the sella is no more competent to contain the pituitary and the tumor, there will be a rupture of the content of the sella into the cranial cavity and or the sphenoidal sinus. When the tumor leaves the limits of the sellar cavity, the universe of the adenoma in terms of headache and ISP are no more the sella, but the cranial cavity, in these conditions there is a decrease in relation of the ISP and headache. If the adenoma grows enough outside the sella (intracranial, intra sphenoidal or intracavernous), the ISP and the headache can be influenced. An important factor involved in the genesis of the headache is the speed of the tumor growth and the ability of the sellar walls to modulate this growth. In general, patients with fast growing tumor confined to the sella (pituitary apoplexy, metastases tumors), are more susceptible to present more headache and ISP than those with slow growing tumor.

Conclusion

Headache is commonly associated with pituitary tumors and may be an incapacitating symptom. Nevertheless we observed an anatomical importance of tumor size, optic chiasm compression, sellar destruction and cavernous sinus invasion in genesis of headache. Participation of biochemical-neuroendocrine factors, mainly in prolactinomas, seems to be an important associated factor in the origin and determination of the severity of pituitary tumor related headache. The ISP may be an important factor in the origin of pituitary headache. Further investigation studies must be done to clarify the relationship between ISP, pituitary tumor and headache.

Conflict of interest None.

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