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Review Article

Bacterial Meningitis Associated with Pituitary Macroadenoma: Systematic Review

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Abstract

Introduction

Bacterial meningitis complicates rarely pituitary macroadenomas. The aim of our systematic review is to study the features of the association between bacterial meningitis and pituitary macroadenoma.

Methods

We conducted a literature search in both MedLine and Google Scholar database from 1967 to October 2016 and reviewed all cases described of the association between bacterial meningitis and pituitary macroadenoma apart from any surgical act and without pituitary apoplexy.

Results

We found 14 articles describing 16 patients aged of 22-69 years old with a male predominance (sex ratio 4.3). Two patients (12.5%) had a well-documented clinical history of pituitary macroadenoma prior to the diagnosis of bacterial meningitis. Rhinorrhea has been found as the most common symptom in six patients (37.5%). Through the CSF culture, bacterial meningitis among patients suffering from pituitary macroadenoma commonly was due to Streptococcus pneumoniae. The examination in 18.75% of cases revealed signs related to pituitary macroadenoma (ophthalmoplegia and blindness). Six patients (37.5%) had received a treatment by dopaminergic agonist alone and 4 patients (25%) were treated with dopaminergic agonist associated with surgical treatment. Surgical treatment consisted of closure of the osteomeningeal breach in 12.5% (2/16) and tumor resection in 31.25% (5/16). Three patients (18.75%) had benefited from tumor resection without prior agonist treatment. The mortality was 12.5% (2/16).

Conclusion

Our systematic review shows that bacterial meningitis represents a rare initial symptom leading to the diagnosis of invasive pituitary macroadenoma.

Keywords:
pituitary macroadenoma; bacterial meningitis; systematic review.

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Introduction

Pituitary macroadenomas (PM) are usually revealed by endocrine disorders such as galactorrhea, menstrual disorders, decreased libido, sexual impotence, gynecomastia, or headaches and visual troubles [1]. Bacterial meningitis (BM) is a rare complication of the PM apart from any surgical act and without pituitary apoplexy with few cases described in the literature. The aim of our systematic review is to study the features of the association between BM and PM.

Methods

We conducted a literature search in both MedLine and Google Scholar database from 1967 to October 2016 using the following keywords: "meningitis" and "pituitary adenoma" or "meningitis" and "macroprolactinoma" or "meningitis" and "pituitary macroadenoma". At the end of our literature search, we found three case series and 16 case reports describing a total of 22 cases of BM complicating a PM apart from any prior surgical act and without pituitary apoplexy (Table I). We included in this systematic review case reports and case series in English and French language that also had data available. We did not include the articles that are not written in English or French language and those that did not have data available. Thus, among the 19 articles found, 14 articles were extracted, examined and included in this systematic review. For each article, the following data were extracted: age, sex, past medical history, clinical presentation, imaging results, cerebrospinal fluid (CSF) results, anatomopathology findings, treatment and evolution.

Table I. reported cases of bacterial meningitis complicating a pituitary macroadenoma apart from any previous surgical intervention and without pituitary apoplexy.

Authors , year , [reference]	Number of patients
Margari et al, 2014 [1]	1
Chentli et al, 2015 [2]	3
Wood et al, 2002 [3]	1
Aslan et al, 2014 [4]	1
Bouchal et al, 2015 [5]	1
Onodal et al, 1992 [6]	1
Stephenson et al, 2001 [7]	1
Tan et al, 2010 [8]	1
Toudou-Daouda et al, 2015 [9]	1
Boscolo et al, 2014 [10]	1
Andrysiak-Mamos et al, 2013 [11]	1
Honegger et al, 2009 [12]	1
Robert et al, 2010 [13]	1
Utsuki et al, 2004 [14]	1
Ciatto, 1978 [15]©	2
Devic et al, 1973 [16]©	1
Ghose et al, 1972 [17]©	1
Laszewski et al, 1990 [18]©	1
Rozsíval et al, 1967 [19]©	1
Total	**22**

© : Cases excluded from the systematic review.

Results

Among the 22 cases of BM complicating a PM apart from any prior surgical act and without pituitary apoplexy, our systematic review had included 16 cases that had available data. Table II summarizes the epidemiological, clinical and paraclinical features of the 16 patients. The mean age of the patients was 40.7 years (range: 22 and 69 years). Thirteen patients (81.25%) were men (sex ratio 4.3). Only 2 patients (12.5%) had a known diagnosis of the PM prior to the diagnosis of BM and none of them had experienced rhinorrhea. One of these two patients had received dopaminergic agonist (cabergoline) therapy prior to the episode of BM. Rhinorrhea was found in 37.5% (6/16) of cases without any cranial trauma or dopaminergic agonist intake. One patient had reported secondary amenorrhoea before the episode of BM.

The most common clinical sign was fever (93.75%), followed by nuchal stiffness (75%; Table II). Other clinical signs were altered consciousness (56.25%), behavioral disorders (6.25%), headaches (50%), vomiting (37.5%), visual troubles (6.25%), photophobia (6.25%), ophthalmoplegia (12.5%).

Table II. epidemiological, clinical and paraclinical features of the 16 patients.

Variables		N (%)
Age, average in year (range)		40.7 (22 - 69)
Males		13 (81.25)
Past medical history	Macroprolactinoma before	2 (12.5)
	Notion of rhinorrhea before	6 (37.5)
	Dopaminergic agonist intake	1 (6.25)
Time of consultation, average in days (range)		2 (A few hours to 4 days)
Duration of hospitalization, mean in days (range)		19 (4 - 35)
Clinical signs	Fever	15 (93.75)
	Nuchal stiffness	12 (75)
	Altered states of consciousness	9 (56.25)
	Behavior disorders	1 (6.25)
	Headaches	8 (50)
	Vomiting	6 (37.5)
	Decreased vision	1 (6.25)
	Photophobia	1 (6.25)
	Ophtalmoplegia	2 (12.5)
Isolated germ in CSF study	Streptococcus pneumoniae	5/7 (71.4)
	Streptococcus oralis	1/7 (14.3)
	Streptococcus mitis	1/7 (14.3)
Prolactinemia, mean in ng (range)		2924,65 (200 - 9000)
Panhypopituitarism		4 (25)
Histological confirmation of the PM		8 (50)
Cerebral imaging practice	CT scan	16 (100)
	MRI	14 (87.5)

N: number, %: percentage. CSF: cerebrospinal fluid. ng: nanogramme. PM: pituitary macroadenoma. MRI: magnetic resonance imaging. CT scan: computed tomography.

The average time of consultation of patients was 2 days (range: a few hours to 14 days). 68.75% of patients had been admitted within 24 hours of the onset of symptoms.

The cerebral CT scan was performed for all patients and 87.5% (14/16) among them underwent cerebral magnetic resonance imaging (MRI) (Table II). The cerebral CT scan revealed PM in the form of an invasive intra- and suprasellar lesional process in all patients (100%). The cerebral MRI was performed as a complement to the cerebral CT scan and confirmed the diagnosis of invasive PM by highlighting the invasion of the sphenoid sinus in 50% (7/14) and the cavernous sinus in 42.86% (6/14) and a

Table III. treatments and outcomes of the 16 patients.

Variables		N (%)	Evolution	
			Favorable N (%)	Death N (%)
Surgical treatment	Tumor resection	7 (43.75)	7 (43.75)	0
	Decompressive craniectomy	1 (6.25)	0	1 (6.25)
	Closure of OB	2 (12.5)	2 (12.5)	0
Dopaminergic agonists		10 (62.5)	10 (62.5)	0
Hydrocortisone		5 (31.25)	4 (25)	1 (6.25)
Levothyroxine		3 (18.75)	3 (18.75)	0

compression of the optic chiasma in 14.3% (2/14). The cerebral MRI also highlighted other radiologic findings such as cerebral venous thrombosis in 7.15% (1/14), cerebral infarction by meningovascularitis in 14.3% (2/14), cortical laminar necrosis in 7.15% (1/14). Histological confirmation of PM was performed in 50% (8/16).

Through the CSF culture, a causative agent was found in 43.5% of cases (Table II). Streptococcus pneumoniae was the most common isolated causative agent in 71.4% (5/7), followed by streptococcus mitis in 14.3% (1/7) and streptococcus oralis in 14.3% (1/7). The hypophysiogram showed hyperprolactinemia in all cases with an average of 2924.65ng/mL (range: 200 and 9000 ng/mL). Panhypopituitarism was associated in 25% (4/16; Table II).

62.5% (10/16) of patients underwent medical treatment based on dopaminergic agonist and the drugs used were cabergoline in 70% (7/10) and bromocriptine in 30% (3/10). Other additional drugs used as described in the articles were levothyroxine-hydrocortisone in 18.75% (3/16) and hydrocortisone in 12.5% (2/16). Half the patients underwent a surgical procedure which consisted of resection of the PM in 62.5% (5/8), closure of the osteomeningeal breach in 25% (2/8), and especially a bifrontal decompressive craniectomy for diffuse cerebral edema in 12.5% (1/8). Table III summarizes the treatments and outcomes of the 16 patients.

The clinical course was favorable overall. The delay of in-patient unit was 19 days (range: 4 and 35 days). Two patients (12.5%) died as described in articles due to diffuse cerebral edema with tonsillar herniation and cortical laminar necrosis.

Discussion

BM is a rare complication of the PM apart from any prior surgical act and without pituitary apoplexy. Our systematic review had analyzed all the reported cases of the association between BM and PM, which had data available and compatible with our selection method. Only 2 patients (12.5%) were diagnosed for PM before the episode of BM [2,3]. The only symptoms identified that could be presumptive signs of the diagnosis of the PM before the episode of BM were rhinorrhea that was found in 6 patients (37.5%) and amenorrhea in one patient (6.25%) [2,4,5,6,7,8].

The clinical presentation was mainly dominated by signs of BM: nuchal stiffness (75%), headaches (50%), vomiting (37.5%), fever (93.75%), and altered consciousness (56.25%). Clinical signs probably related to the PM were decrease of visual acuity (6.25%) and ophthalmoplegia (12.5%). The visual troubles could be explained by compression of the optochiasmatic tract [9]. Ophthalmoplegia is the consequence of the invasion or compression of the oculomotor nerves in the cavernous sinus by the PM [9]. The disturbance of consciousness could also be a sign related to PM by endocrine disorders especially the lackness of corticotropic axis [1,5,9,10].

In terms of physiopathology, the occurrence of BM could be explained by the fact that PM destroy the sellar floor and invade the sphenoid sinus and the meninges creating an osteomeningeal breach

with leakage of the CSF (rhinorrhea) responsible for the bacterial infection of the meninges and cerebral structures [9]. The rhinorrhea can precede the BM [2,4,5,6,7,8] or even be totally unnoticed [1,2,3,9,10,11,12,13,14]. The absence of rhinorrhea in the majority of patients (62.5%) could be explained by the fact that the osteomeningeal breach was clogged by the PM [9,10].

MRI remains the first choice to perform brain imaging not only in the diagnosis of the PM but also in the exploration of its anatomical relationships with neighboring structures. Cerebral MRI, coupled with the prolactin assay, is sufficient to establish the diagnosis of invasive PM. The histological study is performed only when a tumor resection has been performed in the case of compressive PM with visual troubles or disturbed ophthalmologic examination especially fundus examination and visual field [11], or in case of treatment failure with dopaminergic agonists with persistence of hyperprolactinemia [14]. In our study, the histological study has been realized in 2 patients with suspicion of invasive PM to the cerebral CT scan and in whom a cerebral MRI has not been performed [4,6].

Streptococcus pneumoniae was the most common causative agent of BM in our study (71.4%). The other germs were streptococcus oralis (14.3%) and streptococcus mitis (14.3%). This great predominance of streptococcus pneumoniae is due to the fact that this bacterium is very common in the respiratory tract (especially the nostrils) even in man being healthy.

In our study, the minimum value of prolactin is 200ng/mL which is a specific biological element in favor of the diagnosis of macroprolactinoma. Only one case of transient elevation of ACTH with hypercortisolemia associated with hyperprolactinemia was observed in our study [14]. On the other hand, we have underlined 4 cases of panhypopituitarism associated with hyperprolactinemia [1,5,9,10]. The panhypopituitarism would probably be secondary to a compression of the pituitary stem disconnecting the pituitary gland, which is a rare situation in the PM.

Dopaminergic agonists (cabergoline or bromocriptine) represent the first choice treatment of macroprolactinomas without alteration of the ophthalmic examination (fundus examination and visual field). In our study, dopaminergic agonists had allowed a reduction of the size of the PM in 8 patients [1,2,3,5,8,9]. On the other hand, tumor resection was initially performed in 4 patients [4,11,12,14], among which one patient had received a treatment by dopaminergic agonist in a second time [12]. One patient received treatment with a dopaminergic agonist followed by secondary tumor resection [10]. Moreover, the closure of the osteomeningeal breach is not systematic and should be performed only when the leakage of the CSF is important [1]. In our study, six patients had presented episodes of rhinorrhea before the diagnosis of BM, among which only 33.33% (2/6) had benefited from a closure of the osteomeningeal breach [5,8].

The prognosis of the association of BM and PM has been globally good in our study. The mortality rate was 12.5% (2 patients) [6,13]. Death occurred in a clinical picture of cerebral herniation due to diffuse cerebral edema in one patient and in the other patient following a cortical laminar necrosis related to a cerebral hypoxia.

Conclusion

The occurrence of BM secondary to an invasive PM is a rare clinical situation, but of good prognosis in general. Dopaminergic agonists represent the first choice treatment of macroprolactinomas if the ophthalmic examination is normal and if they are sufficient to allow the reduction of the size of the PM and normalization of prolactinemia. Tumor resection is only performed in the case of compressive PM with visual troubles or disturbed ophthalmologic examination (fundus examination and visual field), or when the medical treatment does not allow a significant reduction of hyperprolactinemia or the size of the PM when the latter is not compressive and with normal ophthalmological examination.

Competing Interests

The authors declare that they have no competing interest.

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