

Original Article

Primary empty sella syndrome: Characteristics of the pituitary deficiency. A bicentric case series.

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Publication data:
Submitted: January 2,2020
Accepted: February 28,2020
Online: March 15 ,2020

This article was subject to full peer-review.

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Abstract:

Background and aim

Empty sella is the neuroradiological or pathological finding of an apparently empty sella turcica. The aim of the study was to analyze the clinical, hormonal and radiological characteristics of patients with empty sella and to compare anterior pituitary function in total versus partial primary empty sella.

Methods

The records of 36 patients with primary empty sella were retrospectively analyzed over a 24-years period. The patients were evaluated for pituitary function with basal hormone levels (FT4, TSH, IGF1, FSH, LH, cortisol, ACTH, prolactin) and dynamic testing when necessary.

Results

Our study included 26 women and 10 men with an average age of 47.64 ±15.47 years. Seventy-six per cent of women were multiparous. Fifteen patients were obese. The revealing symptoms were dominated by endocrine signs (52.7%). More than half of our patients complained of headache. Sixty-one of the patients had partial empty sella and the remaining 39% had total empty sella. Two or more pituitary hormone deficiency were found in 41% of cases. Secondary adrenal insufficiency was the most common pituitary hormone deficiency(41.7%).The percentage of hypopituitarism in complete primary empty sella was significantly higher than that in partial primary empty sella (P<0.05).The management was based on hormone replacement therapy in case of hypopituitarism and on analgesic therapy in case of headache.

Conclusion

The diagnosis of PES must be evoked in an obese, multiparous, hypertensive woman presenting with a symptomatology suggestive of a pituitary deficiency or chronic headache. The correlation between pituitary gland volume and the degree of hypopituitarism highlights the importance of the early diagnosis and hormones replacement.

Key words

Primary empty sella; hypopituitarism; diagnosis; management.

Introduction

The term primary empty sella (PES) is a neuro-radiological finding defined as an intrasellar herniation of subarachnoid space through a congenital or acquired defect in the diaphragma sellae, allowing cerebrospinal fluid (CSF) to enter the sella, which is often associated with stretching of the pituitary stalk and some degree of compression and flattening of the pituitary gland against the sellar floor which can cause various degrees of pituitary dysfunction in patients without previous pituitary disorders. The prevalence of PES in the general population varies from 8% to 35% [1,2]. The easier access to the magnetic resonance imaging (MRI), has made PES a frequent incidental finding. Radiologically, the sella is defined as partially empty when less than 50% of it is filled with CSF and the pituitary gland thickness is ≥ 3 mm, or totally empty when more than 50% of the sella is filled with CSF and the gland thickness is <2 mm in diameter [3,4]. Even usually asymptomatic, PES can be associated to serious clinical conditions including different degrees of hypopituitarism and neurological deficits [3]. Several retrospective studies assessed endocrine abnormalities in PES, but few compared the pituitary functions between total and partial PES. Moreover, there is no consensual guidelines for the management of PES.

The aim of our study was to analyze the clinical, hormonal and radiological characteristics of patients with PES and to demonstrate the correlation between the residual gland volume and the degree of the hypopituitarism.

Patients and Methods

The records of thirty-six patients with a diagnosis of PES between 1992 and 2016 seen at the internal medicine A department of Charles Nicolle's hospital of Tunis and at the endocrinology department of the military hospital of Tunis were examined retrospectively, 1 year or more after hospital discharge. Anthropometric, historical, endocrine, neurological, ophthalmological and radiological available data of each patient at diagnosis and during follow-up were analyzed and recorded.

Inclusion criteria

All patients having PES diagnosed by pituitary MRI or computed tomography (CT).

Exclusion criteria

*Subjects with a previous history of congenital or acquired hypothalamic-pituitary or central nervous system diseases.

*Subjects with a history of head trauma.

*Subjects with a previous history of medical, neurosurgical, or radiation treatment for pituitary adenomas or tumors.

*Subjects with ascertained GH and cortisol hypersecretion or patients with prolactin levels > 100 ng/ml for whom the diagnosis of an empty sella secondary to the necrosis of a preexisting pituitary adenoma could not be excluded.

Statistical analysis

All the data were analyzed using statistic program for Social Sciences (SPSS) Program Software version 11.5. Data were expressed as mean standard deviation. The categorical data were assessed by the Pearson chi-square test. Student's t and Fisher's exact tests were used for the comparison of parametric quantitative data. Regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (95% CI) of individual pituitary hormone deficiency between subjects with total and partial PES.

Results

Epidemiology and risk factors

A total of 36 patients were included in this study. Population epidemiological and clinical characteristics are summarized in Table 1. The PES peak incidence was noted between the 51 and 60 years old. Two male patients were aged less than 15 years at the inclusion. Among the female patients with PES, 19 were multiparous. Mean number of pregnancies in the multiparous patients was 5.16 ± 1.83 . Mean body mass index (BMI) was 30.09 ± 7.37 kg/m². Arterial hypertension, type 2 diabetes mellitus and autoimmune hypothyroidism were found in 38.9%, 25% and 8.3% respectively. Only one patient had idiopathic intracranial hypertension. In our patients, neither primary hypoadrenalism nor primary hypogonadism were observed. No significant differences were found among the partial and total empty sella subgroups regarding risk factors of PES (table1).

Clinical presentation

Endocrine signs were the most common presenting symptoms (52.7%). They were dominated by hypocortisolism in females and gynecomastia with erectile dysfunction in males. The two youngest patients presented for delayed growth. PES was found incidentally in 4 cases (11.1%). More than half of our patients complained of headache (52.7%). This headache was variable in localization, severity and duration. It was fronto-orbital, bitemporal or holocranial. The pain was persistent or intermittent and recurrent with a high intensity in most of the cases.

Table 1: Epidemiological and clinical features of patients with primary empty sella

	n=36	Partial PES (n=22)	Total PES (n=14)	P
Age	47.6 \pm 15.4	49.23 \pm 14.9	45.14 \pm 16.4	0.602
F/M	26 / 10	15 / 7	11 / 3	-
BMI	30,09 \pm 7,37	30,25 \pm 8,01	29,87 \pm 6,67	0.415
Multiparity	19 (76%)	13 (59%)	6 (42.85%)	0.412
Obesity	15 (41.6%)	10 (45.45%)	5 (35.7%)	0.347
Overweight	7(19.4)	2(9.1)	5(35.7)	0.72
Hypertension	14 (38.9%)	11 (50%)	3 (21.4%)	0.086
Type 2 DM	9 (25%)	7 (31.8%)	2 (14.3%)	0.236
Headache	19 (52.8%)	13 (59%)	6 (42.85%)	0.342

Endocrine findings

At least one anterior pituitary hormone deficiency was found in 72% of cases. Ten patients did not have any anterior pituitary deficiency at diagnosis. Secondary adrenal insufficiency was the most common hormonal abnormality (41.7 %) followed by hypogonadotropic hypogonadism and central hypothyroidism in 33.3 and 19.4 % of cases respectively. Mild hyperprolactinemia and central diabetes insipidus were also recorded in 19.4% and 5.5% of patients, respectively. The mean prolactin levels were 47.56 ± 18.17 ng/ml.

This hyperprolactinemia was isolated in 2 patients. The somatotrophic axis was not adequately assessed in adult patients with PES so we could not rule out this deficiency. An isolated GH deficiency was diagnosed in the two cases of delayed growth with an absence of response after two GH stimulation tests. In our patients, the percentage of hypopituitarism in total PES was significantly higher than that in partial PES (table 2).

The corticotropin deficiency, gonadotropin deficiency and secondary hypothyroidism were considerably higher in cases with total compared to the cases with partial PES (OR = 8.0 95% CI 1.7–37, OR = 7.2 95% CI 1.51–34.13, OR=15.7 95% CI 1.63–152.17, respectively).

Ophthalmological findings

Visual disturbances were noted in 12 patients including decrease of visual acuity, papilledema on fundus examination and visual field defects in four, five and three patients, respectively.

Radiological findings

The diagnosis was confirmed by CT of the pituitary in 4 patients and by pituitary MRI in 32 cases. Only one patient underwent both exams. Sixty-one of the patients had partial empty sella and the remaining 39% had total empty sella (Figure 1).

The pituitary stalk was stretched in 3 patients among them only one had central diabetes insipidus and another had hyperprolactinemia. Other radiological abnormalities on MRI were associated with PES: an absence of the normal posterior pituitary bright signal in 2 patients consulting for polyuria and an optic chiasma ptosis in a patient with campimetric defect (Figure 2).

Treatment

Medical treatment

The medical treatment of PES was based on the hormone replacement therapy in case of pituitary deficiency and pain reliever in case of headache. Among the patients with hypopituitarism, early hormone replacement has been provided in 79.6% of cases.

The two children with isolated GH deficiency were submitted to Recombinant human GH treatment was prescribed in two cases. The patients with symptomatic

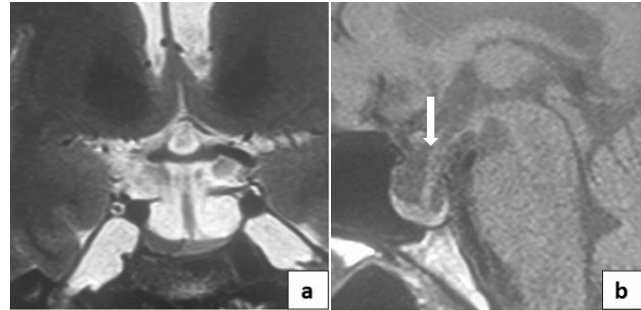


Figure1: total empty sella with MRI features: CSF in the sella with pituitary stalk deviation

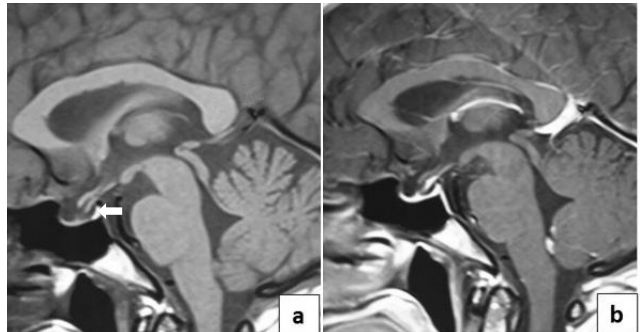


Figure2: MRI features of total empty sella with optic chiasma herniation

Table 2: hormonal disorders: partial vs total PES

	n=36	Partial PES (n=22)	Total PES (n=14)	p
Corticotropin deficiency	15(41.7%)	5 (22.7%)	10(71.4%)	0.005
hypothyroidism	7(19.4%)	1 (4.5%)	6(42.8%)	0.008
Gonadotropin deficiency	12 (33.3%)	4 (18.2%)	8 (57.1%)	0.024
Hyperprolactinemia	7 (19.4%)	3 (13.6%)	4 (28.6%)	0.27

hyperprolactinemia underwent bromocriptine in four cases and cabergoline in one case. Objective improvement of symptoms was obtained in all cases. The two patients with central diabetes insipidus were submitted to desmopressine intranasal spray treatment at a dose of 25 to 30 µg per day. That permitted to normalize plasma and urinary osmolarity and serum electrolytes.

Surgical treatment

Only one patient underwent a ventriculo-peritoneal shunt for idiopathic intracranial hypertension (IIH) resistant to medical treatment.

Evolution

Twenty-nine patients (80.5%) were followed for an average duration of 4.98 ± 4.18 years. Five patients had persistent headache.

Only one patient, initially asymptomatic, complained of headache appeared after 5 years of follow up. The anterior pituitary function was stable in the initially asymptomatic patients. Only one case of central hypothyroidism was

diagnosed after 6 months in a woman who had already a corticotropin insufficiency. Prolactin deficiency was noted after 3 years of follow-up in a patient with initial gonadotropic and corticotropin insufficiencies. Imaging regular follow up was performed in 9 patients. It revealed pituitary thinning with optic chiasm ptosis in one patient initially diagnosed with a partial empty sella. The ophthalmological follow up was performed in 7 symptomatic patients. It remained unchanged in 3 patients and revealed decreased visual acuity in 2 patients and visual field defect in 2 others.

Discussion

PES is a common condition, reported in up to 35% of radiological series, is typically more prevalent in females [4]. This entity pathogenesis is still controversial. Several hypotheses have been proposed, including a congenital defect of the sellar diaphragm associated with suprasellar increase in the intracranial pressure or volumetric changes in the pituitary gland [5]. Several studies demonstrated an obvious relationship between obesity and PES. The morbid obesity may induce hypercapnia which causes chronic CSF hypertension. That may lead to the intrasellar herniation of the suprasellar subarachnoid space in patients with hypoplastic diaphragma sellae [6]. Some authors have documented an objective relationship between intra-abdominal, intrathoracic and intracranial pressure in obese patients [5,6].

Our data are substantially in line with what was reported in the literature as 41.6% of our patients were obese. Our results also demonstrated that multiparity may contribute to the development of PES. The enlargement of the pituitary during pregnancy may lead to weakening of the sellar diaphragm and predispose to intrasellar herniation of cerebrospinal fluid [7]. More than three quarter of our female cases were multiparous.

Autoimmunity may also have a role in the development of PES that has been suggested to be a consequence of lymphocytic hypophysitis. Caturegli et al detected the presence of anti-pituitary hormone antibodies in 22-42% of PES patients [8].

Other endocrine diseases were described to be associated to PES such as autoimmune primary hypothyroidism, primary adrenal insufficiency and primary hypogonadism. This relationship may be explained by the pituitary hyperplasia seen in case of multiple hormones deficiencies [9]. In our study, the prevalence of autoimmune hypothyroidism was 8.3%. No cases of primary adrenal insufficiency or primary hypogonadism were found. PES has been reported to be associated with several common endocrine abnormalities. Recent studies have demonstrated that pituitary hormone deficiency was present in about 8 to 60% of PES cases [10]. Seventy five percent of our patients had pituitary dysfunction at the PES diagnosis.

The pituitary dysfunction may be due to the chronic compression of the pituitary gland and the pituitary stalk by CSF. Hyperprolactinemia and GH deficiency have been mentioned as the most prevalent hormone abnormalities in patients with PES [11]. In our series, corticotropin deficiency was the most common pituitary insufficiency. The high incidence of GH deficiency in patients with PES might be related to the peripheral disposition of somatotropes within the pituitary gland. That makes these cells more vulnerable to increased intrasellar pressure. Other authors suggested that obesity might decrease spontaneous or induced GH secretion [12]. In pediatric series, GH deficiency represents the most common isolated pituitary deficiency reaching up to 64% of children with PES [13]. The Hyperprolactinemia is usually moderate in PES (less than 100 ng/ml). The incidence is estimated at 10 to 37.5 %. The pituitary stalk compression by CSF may result in a decrease in the Prolactin inhibiting factor (dopamine). This could explain the hyperprolactinemia in PES patients. However, the diagnosis of prolactinoma should be kept in mind and evoked for the prolactin levels > 150 ng/ml [14]. In our study, hyperprolactinemia was present in 19.4 %. Among them, only one patient had a stretched pituitary stalk on MRI. Previous reports indicated that hypopituitarism was not related to the residual gland in PES. Our results are concordant with many other studies that demonstrated the correlation between the residual pituitary gland volume and hypopituitarism. In all cases of PES, appropriate and exhaustive endocrine assessment should be done regardless of the type of PES on neuroimaging findings.

Headache is one of the most prevalent symptoms in PES, reported in about 60 to 80 % of cases. Most of the authors suggested that pain is due to the traction on vascular-meningeal structures in the sellar cavity [15]. Visual disturbances have been reported in only 1.6 to 16 % of cases with PES. The most reported symptoms are decreased visual acuity and visual field defects (tunnel vision) which usually consists in, bitemporal hemianopsia or quadrantanopia [16]. These troubles could be explained by the intrasellar herniation of the optic nerve or by its decreased blood supply. Severe complications of CSF stasis such as papilledema, optic atrophy or blindness has been reported. A systematic ophthalmological examination in patients with PES is always recommended.

The treatment of patients with PES includes appropriate hormonal supplementation in patients with endocrine dysfunction, dopamine agonists in patients with symptomatic hyperprolactinemia and pain killers in patients complaining of headache. Asymptomatic PES patients are candidate for regular follow up to rule out any regarding hormonal, ophthalmological disorder onset [17].

Surgical indications for symptomatic PES are controversial and rare. Visual disturbances and cerebrospinal rhinorrhea are the main indications for surgery. CSF shunt placement is effective to treat PES associated to IIH [18]. In our study, a ventriculo-peritoneal shunt was performed in an obese patient with IIH resistant to medical treatment. A remission of headache and papilledema was obtained after surgery. This study highlights PES as progressive disease that induce various hormonal, visual and neurological disorders. The hormonal disorders can appear years after the diagnosis. The gravity of the symptoms looks related to the residual functional gland volume. A regular monitoring with clinical, hormonal, ophthalmological and radiological assessment is mandatory [19,20]. The results of our study should be proved on a larger comparative prospective trial.

Conclusion

PES should be evoked more often in an obese, multiparous, hypertensive, diabetic woman with symptomatology suggestive of pituitary dysfunction, chronic headaches or visual disturbances.

The diagnosis is based on hypothalamic-pituitary MRI. The size of the residual pituitary gland is correlated with the degree of hypopituitarism. Thus, a prompt endocrine, neurologic, and ophthalmologic evaluation at the time of initial presentation is recommended.

Early hormones replacement therapy relieves the symptoms and improve the prognosis. Asymptomatic patients should be regularly followed even in the absence of pituitary dysfunction.

Conflict of interest

The authors declare that there is no conflict of interest.

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