Primary Empty Sella (PES): A review of 117 cases

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ABSTRACT

Introduction: The term Primary Empty Sella (PES) makes reference to the herniation of the subarachnoid space within the sella in patients with no history of pituitary tumor, surgery or radiotherapy. Although it is not usually associated with endocrine abnormalities, different degrees of hypopituitarism and mild hyperprolactinemia have been reported.

Objective: To retrospectively analyze clinical data, radiological and biochemical findings from records of 117 patients with a diagnosis of PES.

Patients and Methods: We studied 117 patients; 98 females (48 ± 14.9 yr). Diagnoses were made by Magnetic Resonance Imaging (n = 115), and Computed Tomography (n = 2). The anterior pituitary function was evaluated by basal hormonal measurements.

Results: The reasons for ordering pituitary scans were: headaches (35 %), clinical and biochemical suspicion of pituitary deficiency (22 %), visual disturbances (11 %), abnormalities on the plain radiograph of the sella (11 %) hyperprolactinemia (2,6 %), others (18.4 %). Forty-eight point nine per cent of women were multiparous. Headaches, obesity, hypertension and thyroid autoimmunity were found in 60 %, 67 %, 24.5 % and 22.5 % of the studied population respectively. Hyperprolactinemia (< 50 ng/ml) was present in 6.1 % of women and in 15.8 % of men. Twenty seven percent of our patients had some degree of hypopituitarism, more common in the male population.

Conclusions: PES was most commonly found in middle-aged multiparous women. In most patients, PES was discovered as an incidental finding on imaging studies, while in a quarter of patients PES was found during diagnostic evaluation of anterior pituitary deficiency, which was more common in men.

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Key words: empty sella, arachnoidocele, hypopituitarism

INTRODUCTION

The term empty sella or arachnoidocele has been defined as the herniation of the subarachnoid space within the sella, associated with elongated pituitary stalk and flattening of the pituitary gland against the floor of the sella¹,².

There are two types of empty sella. The first one and most common results from a pathological process that may or may not be neoplastic in nature, although it most commonly occurs after spontaneous regression (apoplexy) or treatment (surgery, radiotherapy or drug therapy) of a pituitary adenoma². It may also be secondary to postpartum pituitary necrosis (Sheehan’s Syndrome) or to lymphocytic hypophysitis. These cases are known as “Secondary Empty Sella” (SES).

The second type of empty sella, which is being addressed in this paper, is that in which there has been no previous known pathological process. It is known as “Primary Empty Sella” (PES) and both its pathogenesis and clinical significance are a matter of discussion³,⁴.
PES may be a radiological finding in asymptomatic patients or it may be associated with variable clinical conditions such as neurological, ophthalmological and/or endocrine disturbances \(^5\). Increased intracranial pressure associated with defects of the sellar diaphragm are considered as etiopathogenetic factors in PES \(^6\). Both would be present in obesity and in multiparous women, conditions that are commonly associated with PES.

Empty sella is defined as partial or total when less or more than 50% of the sella is filled with CSF, respectively, with the pituitary being < 2 mm in the latter case \(^1\).

The widespread use of Computed Tomography (CAT) and Magnetic Resonance Imaging (MRI) has made PES a common incidental finding. According to data obtained from autopsies and neuroradiological exams, the presence of empty sella ranges from 5.5 % to 35%, with a female/male ratio of 4/1 \(^1\)-\(^4\).

The aim of this paper was to report the clinical experience obtained from a multicenter retrospective study conducted in Buenos Aires, in which some of the hospitals that make up the Department of Neuroendocrinology of SAEM (Argentine Society of Endocrinology) participated by providing new data that may contribute to the diagnosis, therapy and long-term follow-up of patients with a diagnosis of PES.

**PATIENTS AND METHODS**

We retrospectively evaluated 117 patients (98 females, 19 males) from different sites in the city of Buenos Aires. All patients had PES diagnosed by MRI (n = 115) or CAT (n = 2). Mean age at diagnosis was 48 ± 14.9 years. A group of patients (n = 56) provided a plan radiograph of empty sella ordered as part of routine endocrine testing.

Clinical data were obtained from medical records at each site according to individual diagnostic criteria.

Endocrine, ophthalmological, and radiological available data of each patient at diagnosis were included.

Criteria for exclusion were: history of either hypothalamic-pituitary or central nervous system diseases; medical, surgical, and radiation treatment for pituitary lesions; GH and cortisol hypersecretion or patients with prolactin levels greater than 100 ng/ml, to rule out the possibility of PES.

Baseline endocrine evaluation was performed in most patients: free T4, TSH, ATPO, cortisol, LH, FSH, estradiol, testosterone (males), prolactin, GH, IGF 1 (age- and gender-adjusted). Hormone measurements were performed using commercially available kits used in routine testing at the labs of the different sites. TRH-TSH test was performed to rule out subclinical primary hypothyroidism and ACTH test was performed to rule out secondary adrenal insufficiency. No dynamic stimulation tests were performed for evaluation of the somatotropic axis.

Results were expressed as mean ± SEM.

**RESULTS**

Of the 117 patients studied, 98 were females and 19 were males (F/M ratio: 5/1). Total empty sella was documented in 75 patients by imaging of the sellar region, while partial empty sella was reported in 42 patients (Fig 1 and 2).

An enlarged sella was found in 45 of 56 patients on plain radiograph, which led to the subsequent MRI request in many of those patients. Imaging of the sellar region was ordered for different reasons: headaches (35%), clinical and biochemical suspicion of pituitary deficiency (22%), visual disturbances (11%), abnormalities on the plain radiograph of the sella (11%), and hyperprolactinemia (2.6%). Other reasons included
dizziness, seizures, rhinorrhea, loss of consciousness, head injury and galactorrhea.

Sixty-two point two percent of women had at least one pregnancy, while 48.9% reported multiple pregnancies. Visual disturbance was found in 17/65 patients, including scotoma, quadrantanopia and hemianopsia. Two patients had papilledema on fundus examination.

We found associated clinical conditions and diseases such as: headache (60%), hypertension (24%), thyroid autoimmunity (22.5%) (7/31) and obesity (67.6%) (48/71). We found hyperprolactinemia in 6.8 % (6/88) of females and in 15.8 % (3/19) of males. Mean PRL was 11.6 ± 9.4 ng/ml (range 1.3-47) in the whole population, with no differences according to gender.

As regards the anterior pituitary function, 27% (n = 32) had some degree of hypopituitarism: 17 patients had panhypopituitarism (one with diabetes insipidus) and 15 had an isolated deficiency. Of these 15 patients, 11 had hypogonadotropic hypogonadism, 2 had secondary hypothyroidism, 1 had secondary adrenal insufficiency and 1 had diabetes insipidus. IGF! Was consistent with adult GH deficiency (AGHD) in 5/6 patients with panhypopituitarism. When analyzing the population according to gender, some degree of hypopituitarism (n = 19) was present in the male population in 72% of cases, and only in 19% of females.

AGHD was not evaluated by the standard stimulation tests in patients with isolated deficiencies or in those with no evidence of pituitary insufficiency, as they had no clinical symptoms consistent with this condition.

When correlating clinical findings with imaging studies, we found that of the patients with some degree of hypopituitarism (n = 32) 66% had total PES and 34% had partial PES, but of the total number of patients without pituitary insufficiency (n = 85), 75% had total PES.

DISCUSSION

Empty sella is a common finding in autopsies and neuroradiological exams, ranging from 5.5 to 35%, and most commonly reported in females (1-3,4).

In our study, we have found 98 females and 19 males with PES (5/1), confirming a higher prevalence in the female population.

Pregnancy could promote the onset of PES. The pituitary volume doubles during pregnancy, particularly in the case of multiple pregnancies (7). This may contribute to the herniation of subarachnoid space in case of hypoplastic diaphragm sellae and/or CSF hypertension, if moderate and temporary (1,6). Our data show a high prevalence of PES in females with at least one pregnancy, while 48% had multiple pregnancies.

PES has been associated with obesity in different publications (8,9). It is believed that morbid obesity may induce hypercapnia which can be related to chronic CSF pressure elevation and may induce herniation of the suprasellar subarachnoid space (3,10). A clear relationship has been documented between intra-abdominal, intrathoracic and intracranial pressure in obese patients (11). Our data suggest a close relationship between obesity and intrasellar arachnoidocele, as 2/3 of the patients evaluated were obese.

PES has also been reported in association with several endocrine autoimmune diseases (12) and PES itself has been suggested to be the consequence of lymphocytic hypophysitis (2,13). In our study, we found a rate of thyroid autoimmunity somewhat higher than that reported in the general population; however, given the scarce data obtained from this retrospective study, we cannot establish a conclusive correlation.
In this study, increased sellar diameters on plain radiograph of the sella turcica was a common finding in a large number of patients with PES (80%), which could be explained by the chronic pressure of CSF on bone structures.

Headache is one of the most predominant symptoms in PES, reported in 60% to 80% of cases \cite{2,5}, similar to our findings. It is, in turn, the most common reason that imaging studies are performed, often leading to the incidental finding of PES. As it is a very common symptom in the general population, the relationship between headache and PES could be casual in some patients. However, in patients with PES headache may be hypothesized to be caused by traction on vascular-meningeal structures in the sellar cavity, although there is no conclusive evidence \cite{14}.

Although the term PES refers to herniation of the subarachnoid space within the sella, herniation of the suprasellar visual system and the anterior-inferior region of the third ventricle may be occasionally observed \cite{15}. Visual disturbances have been reported in 1.6 to 16% of cases \cite{2}. Visual defects may be severe, and usually include decreased visual acuity, visual field defects, tunnel vision, bitemporal hemianopsia and quadrantanopia. Our findings show that 11% of our patients were diagnosed with PES after presenting at the ophthalmologist for visual disturbances. However, a larger number of patients experienced some visual abnormality when they were studied, although we cannot show a causal relationship between PES and the visual disorders found.

Classically, pituitary function was reported as normal in these patients \cite{16, 17}. There is evidence that the anterior pituitary function disorders most commonly associated with PES are hyperprolactinemia and GH deficiency; some degrees of hypopituitarism may also be found, ranging between 8 and 60% \cite{18, 19}. These events may be explained by the chronic compression of the pituitary gland and the pituitary stalk by CSF \cite{3}. In our study, 27% of patients had some degree of hypopituitarism, half of them with complete deficiency. It is interesting to note that, considering the male population (19 males), 72% had some degree of pituitary insufficiency, versus 19% in the female population. This might be partly due to the larger number of females with PES found in this study.

GH deficiency has been postulated to be an early event in patients with PES, which could be related to the anatomical disposition of somatotrophs, which would render them more vulnerable to increased intrasellar pressure. However, other authors postulate that obesity might play a central role because of its known action in decreasing GH secretory reserve. Del Monte et al found a lower GH response after Arginine / GHRH stimulation in a group of patients with PES with no evidence of other pituitary deficiencies, although they could not rule out the influence of overweight present in most patients \cite{3, 18}.

In our study, we found AGHD in 6/7 patients with panhypopituitarism evaluated by IGF1 measurement. This can be considered as a reliable diagnostic test in patients with 3 or more deficiencies \cite{20}. The somatotropic axis was not studied in all other patients. A larger number of patients might be biochemically diagnosed with AGHD, mainly those with isolated deficiencies. However, stimulation tests such as the insulin-induced hypoglycemia test are not standard of care in adults and, unfortunately, GHRH or GH-releasing peptide (GHRP) is not available in our country; glucagon test is not standard practice yet in our setting.

Hyperprolactinemia has been commonly reported in association with PES. Its incidence ranges from 10 to 37.5% depending on the literature and it has been proposed as the most commonly impaired hormone in PES \cite{1-3, 9}. Pathophysiology is related to pituitary stalk compression secondary to increased CSF pressure in the suprasellar cistern, leading to a decrease in the PRL-inhibiting factor, dopamine. PRL levels are often below 100 ng/ml. In our study, elevated PRL levels were on average 50 ng/ml, in 15.8% of males and in 6.1% of females.
The presence of total or partial PES does not appear to be strictly correlated with the degree of hypopituitarism \(^{(3)}\). Our study supports this concept, since of the 32 patients with some degree of hypopituitarism, 66% had total PES and, conversely, 72% of total PES corresponded to subjects with no documented pituitary deficiencies.

Treatment of patients with PES consists in appropriate hormonal substitution for the detected deficits and correction of hyperprolactinemia with dopamine agonists in patients with symptoms of this condition \(^{(1)}\).

In patients with signs and symptoms of severe intracranial hypertension, disabling headache, visual alterations or CSF rhinorrhea, neurosurgical treatment is clearly indicated \(^{(21)}\). Asymptomatic patients may just remain under observation, as they are unlikely to develop hormonal and radiological changes during follow-up. However, because of the theoretical risk of progression, a regular endocrine, neuro-ophthalmological and radiological reevaluation is recommended in the literature published to date \(^{(19)}\).

**CONCLUSIONS**

PES is a multifaceted condition ranging from asymptomatic presentation to patients with multiple pituitary insufficiency and/or neuro-ophthalmological disturbances. This might reflect the heterogeneity of its pathogenesis. In our study, PES was more common in middle-aged multiparous women. In most cases, PES was incidentally discovered by imaging studies, while in 27% of patients, it was found during the diagnostic evaluation of anterior pituitary deficiency, which was more common in males. Therefore, patients with PES should undergo endocrine and neuro-ophthalmological evaluations given the high incidence of this disorder.

![Fig. 1 a. MRI coronal view of total PES. B MRI sagittal view of total PES.](image-url)
REFERENCES


