DIAGNOSIS OF ENDOCRINE DISEASE

Primary empty sella: a comprehensive review

S Chiloiro¹, A Giampietro¹, A Bianchi¹, T Tartaglione², A Capobianco³, C Anile⁴ and L De Marinis¹

¹Pituitary Unit, Department of Endocrinology, ²Institute of Radiology, ³Institute of Ophthalmology, and ⁴Institute of Neurosurgery, Catholic University of the Sacred Heart, Agostino Gemelli Foundation, Rome, Italy

Abstract

Primary empty sella (PES) is characterized by the herniation of the subarachnoid space within the sella, which is often associated with variable degrees of flattening of the pituitary gland in patients without previous pituitary pathologies. PES pathogenetic mechanisms are not well known but seem to be due to a sellar diaphragm incompetence, associated to the occurrence of upper sellar or pituitary factors, as intracranial hypertension and change of pituitary volume. As PES represents in a majority of cases, a neuroradiological findings without any clinical implication, the occurrence of endocrine, neurological and ophthalmological symptoms, due to the above describes anatomical alteration, which delineates from the so called PES syndrome. Headache, irregular menses, overweight/obesity and visual disturbances compose the typical picture of PES syndrome and can be the manifestation of an intracranial hypertension, often associated with PES. Although hyperprolactinemia and growth hormone deficit represent the most common endocrine abnormalities, PES syndrome is characterized by heterogeneity both in clinical manifestation and hormonal alterations and can sometime reach severe extremes, as occurrence of papilledema, cerebrospinal fluid rhinorrhea and worsening of visual acuity. Consequently, a multidisciplinary approach, with the integration of endocrine, neurologic and ophthalmologic expertise, is strongly advocated and recommended for a properly diagnosis, management, treatment and follow-up of PES syndrome and all of the related abnormalities.

Correspondence should be addressed to L De Marinis
Email laura.demarinis@rm.unicatt.it

Introduction

Empty sella is characterized by the herniation of the subarachnoid space within the sella, which is often associated with variable degree of flattening of the pituitary gland (¹, ²). Empty sella is classified as primary or secondary (³). Primary empty sella (PES) is defined in cases with unknown etiology, after excluding history of previous pituitary pathological condition such as previous surgical, pharmacological or radiotherapy treatment of the sellar

Invited Author’s profile
L. De Marinis is an Associate Professor and Chief of the Pituitary Unit at the Department of Endocrinology of Agostino Gemelli Foundation, Catholic University of the Sacred Heart, Rome, Italy. Her research focuses on neuroendocrine and pituitary physiology in relation to dependent glands and to neoplastic pathology of the hypothalamus–pituitary region, with respect to the physiology of the pituitary hormonal secretion in normal subjects and in patients with pathologies of this complex region, such as GH-, ACTH- and PRL-secreting pituitary adenomas, not functioning pituitary adenomas, craniopharyngiomas, teratomas, empty sella syndrome and primary autoimmune hypophysitis. She studied the genetic background, prognostic marker, efficacy and safety of the different treatments both in pituitary neoplasia and in neuroendocrine tumors.
region (3). Instead, secondary empty sella (SES) can occur following successful trans-sphenoidal pharmacological or radiotherapy treatment or trans-sphenoidal neurosurgery of pituitary tumors; it can lead to spontaneous necrosis (ischemia or hemorrhage) of chiefly adenomas; can result from pituitary infectious processes, pituitary autoimmune disease or brain trauma (4). Moreover, SES can develop in patients who have undergone surgical procedures, radiotherapy and pharmacological treatments of brain tumors, not located in the pituitary fossa (5); particularly in older patients affected by larger brain neoplasia and meningiomas (5).

**History**

The term ‘empty sella’ was first used by Bush in 1951 (6) to describe ‘a peculiar anatomical condition, observed in 40 of 788 human cadavers, particularly females, characterized by a sella turcica with a diaphragma sellae incomplete or that forms only a small peripheral rim, with a pituitary gland not absent, but flattened in such a manner as to form a thin layer of tissue at the bottom of the sella turcica’. In the following years, more details were reported. Particularly Kaufman (7), in 1968, speculated that ‘…empty sella is a distinct anatomical and radiographic entity, function of an incompleteness of the diaphragma sellae and of the cerebrospinal fluid (CSF) pressure, normal or elevated … The role of the normal fluctuations of CSF pressures and the effect of a superimposed prolonged increase in CSF pressure were related to the anatomic changes involving the bony wall of the <empty sella>’.

**Epidemiology of PES**

Epidemiology data of PES are strongly influenced by collection methods. Particularly, at autopsy, PES is described as incidentally finding in approximately 5.5%–12% of cases (6, 7). Instead, at neuroimaging, the overall incidence of empty sella has been estimated at 12%. In clinical practice, according to different series, PES is reported in around 8–35% of the general population (3, 8, 9, 10), with a female-to-male ratio of 5:1 (8). In fact, a large prevalence of PES results among women with a history of at least one completed pregnancy in their physiological history (11). The peak incidence of PES occurs between 30 and 40 years, being sometimes early in women than that in males. PES in children occurs less frequently than in adults and is frequently associated to hypothalamic–pituitary dysfunction, genetic disorders or perinatal complication, as Turner syndrome, Moyamoya disease, Bartter’s syndrome, nevoid basal cell carcinoma syndrome, Hunter syndrome, Prader–Labhart–Willi syndrome, Alstrom syndrome, Meniere’s Disease and Erdheim–Chester disease (12, 13, 14, 15, 16, 17, 18).

**Pathogenesis of PES**

PES etiology is not clear. The possible involved pathogenetic mechanisms are not well known. Numerous etiopathogenetic hypotheses have been developed and included the incomplete formation of the sellar diaphragm and the occurrence of upper sellar factors (as CSF’s pulsatility, stable or intermittent increase in intracranial pressure) or the occurrence of pituitary factors (as variation in the pituitary volume) (Fig. 1).

**Sellar diaphragm deficiency**

The sellar diaphragm is a deflection of the dura mater, which separates the suprasellar cistern from the pituitary fossa, also called sella turcica. This diaphragm...
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also allows the pituitary stalk to pass through a very small opening in its center. Incompetence of the sellar diaphragm is considered crucial in the formation of PES and has been demonstrated in 22–77% of cases, while a total absence of diaphragm sella has been reported in 20.5% of normal subjects (20). Increased pressure in the suprasellar subarachnoid space or pituitary volume reduction predispose to the development of an intrasellar subarachnoid hernia. When the sellar diaphragm is incomplete, an unobstructed pathway exists between the chiasmatic cistern and the pituitary fossa, allowing the unopposed brisk pulsatile movements of the CSF to enter the sella turcica. These pulsations slowly flatten the pituitary gland into the floor of the sella and may occasionally erode through the bony wall of the sella into the sphenoid sinus, producing CSF rhinorhea (21). However, most of these defects alone do not result in herniation of the subarachnoid space, and this confirms that the anomaly of the sellar diaphragm is essential for the development of PES, although other factors seem to be relevant as well.

Upper sellar factors

The role of intracranial hypertension in the genesis of PES has been proposed by many authors. Various intracranial conditions that elevate CSF pressure have been associated with PES, including hydrocephalus, thrombosis, meningitis, brain tumors and Arnold–Chiari malformations (22). Up to 94% of patients affected by intracranial idiopathic hypertension (IIH) also had empty sella (3). IIH, also known as pseudotumor cerebri, is a syndrome of unknown etiology that results in elevated intracranial pressure, in the absence of intracranial mass lesion or hydrocephalus. IIH can be due to impaired CSF absorption, increased CSF secretion, increased cerebral hemodynamics and, at least, increased cerebral capillary permeability (22). Impaired circulation and dynamics of CSF were found up to 77% of patients affected by PES (3): impaired CSF absorption at the arachnoid villi has been proven in 80–84% of patients with PES (3), leading to the elevation of CSF pressures and, subsequently, the herniation of meninges and CSF, through an incompetent sellar diaphragm.

In some cases, normal pulsations of CSF are sufficient to produce the empty sella in the presence of a deficient diaphragm sellae; in fact, in some patients increase of intracranial pressure occurred only during sleeping (3). The spectrum of intracranial hypertension probably begins with silent, milder and intermittent form that evolves in empty sella and ends with more severe forms of IIH, characterized by papilledema, severe headache and visual field symptoms. This would explain why, only in some cases (from 8 to 15%), empty sella progress to develop IIH, but conversely up to 94% of IIH-affected patients already carried an empty sella.

PES has been reported to be associated with obesity and hypertension (23), particularly in females (8). In various series of PES, the percentage of obese hypertensive females achieved 70–80% (24). BMI values are positively correlated to the occurrence on IIH (25). The link between obesity, systemic hypertension and PES is not completely understood, but alterations in the sellar diaphragm and stable or intermittent increase of intracranial pressure may play an etiologic role in the development and maintenance of PES in obesity. In fact, in obese patients with hypercapnia and obstructive sleep apnea syndrome (OSAS), intermittent or persistent elevation of intracranial pressure was described. Moreover, it was postulated that central obesity raises intra-abdominal pressure, with a consequent increase of both pleural and cardiac filling pressures, which obstructs venous return from the brain, leading to increased intracranial venous pressure and intracranial pressure (26, 27, 28). One other mechanism proposed is that obesity, directly or through cytokines and adipokines, can induce the activation of the 11β-HSD1 enzyme, which increases the cortisol production. Cortisol excess increases the intracranial pressure, through the increment of CSF production and through the reduction of CSF drainage (29). Moreover, obesity is associated to thrombophilic- and fibrinolytic coagulator disorders, which could induce microvascular thrombosis and, consequently, reduction of CSF resorption and increase of intracranial pressure (30, 31, 32).

Pituitary factors

Various factors are associated with pituitary gland volume changes, which first determines an expansion and then a reduction of the suprasellar subarachnoid space. If there is no corresponding reduction of both pituitary gland and sella turcica volume, a space can be created, which can allow suprasellar chiasmatic cistern herniation, in cases of hypoplastic diaphragm sellae and in cases of CSF hypertension, even if moderate and temporary.

Increase in the size of the pituitary gland is observed during pregnancy and lactation, when pituitary gland volume can duplicate, enlarging the sella turcica (33). Instead, in women in the fourth decade of life,
pituitary involution is associated with menopause, which explains why PES syndrome predominates in middle-age women. On some occasions, in cases of primary hormonal deficiency (such as primary hypothyroidism, primary hypoadrenalism and primary hypogonadism), a compensatory pituitary hypertrophy occurs (20). At least, also in hypophysitis, which represents an emerging and more frequently diagnosed disease (34), pituitary hyperplasia could evolve in empty sella, as last stage of disease, as suggested by the presence of antipituitary antibodies in around 6% of PES cases (35).

**Presenting clinical manifestations**

PES is often incidentally discovered and represents a relatively common finding in autopsy (5–23%) (6, 7) and in radiological imaging (8–35% in the general population) (36, 37, 38, 39). Empty sella is present in approximately 70% of patients with IIH (40), representing the most commonly described imaging sign in the setting of IIH. In contrast, the incidence of IIH is relatively rare, estimated at approximately 1 case per 100,000 individuals. Therefore, most patients showing an empty sella turcica on imaging will not have IIH. Consequently, PES can be an incidental radiological finding and may usually not present symptoms (41). Instead, when PES is associated with endocrine, neurologic, ophthalmologic and psychiatric symptoms (caused by be above anatomic alteration), the picture of 'primary empty sella syndrome' (PESS) is configured (8). Headache, menstrual irregularities, galactorrhea, hirsutism and sterility are the most common clinical manifestation in PES syndrome (8). Particularly, headache and obesity are considered the most common clinical manifestations respectively in men and in women (3). Occurrence and frequency of signs and symptoms are influenced according to the series and typologies of symptoms for which patients referred to medical attention.

**Endocrinological picture**

The clinical picture in patients with PES is often quite complex and it is not always possible to differentiate symptoms and biochemical findings that are the consequences of the empty sella from those casually found that are merely the reason for medical referral. Therefore, the same symptom may likely be a direct consequence or casually found in patients with PES.

Overweight and obesity involve respectively 73% and 14% of PES-affected patients and, in particular, females: in fact, around 50% of females with PES presents obesity (3).

Irregular menses (hypo, hyper, oligo, poly, amenorrhea, anovular cycles or short luteal phases, etc.) were reported by 40%, galactorrhea by 26% and hypertrichosis by 18% of female patients (3). Instead, among male patients, sexual disturbances were reported in around 53% and gynecomastia in around 12% of cases (3).

Endocrine abnormalities are documented in around 19% of patients (8). Insufficient glandular secretion can be caused by the compression of the pituitary parenchyma against the sellar cavity walls, associated to pituitary stalk posteriorly stretched and attracted down to the thin residual pituitary. This insufficiency can be of varied degrees, ranging from panhypopituitarism with a prolactin (PRL) deficit, to hypopituitarism or isolated hormonal deficit, with hyper or normal PRL value. From the revision of papers published in the last 20 years (3, 8, 11, 42, 43, 44, 45, 46), GHD represents the most frequent pituitary deficit, both in the adult and pediatric population, occurring between 4% and 57.1% of PES syndrome cases. Instead, a similar frequency is identified for secondary hypoadrenalism, hypothyroidism and hypogonadism, which ranges from 2.3 to 32% of PES syndrome cases. At least, hyperprolactinemia is documented in 7–10% of PES syndrome affected patients. Almost half of the patients had a PRL value between 50 and 100µg/L (median prolactin level: 31 µg/L) (8). Furthermore, it must be noted that menstrual irregularities (hypo, hyper, oligo, poly, amenorrhea, anovular cycles or short luteal phases) may also occur while there is a normal PRL level: this can be explained as hypersensibility to normal PRL values or transient hyperprolactinemia, which are not possible to observe with a single basal blood sample. In fact, an alteration of PRL circadian rhythm has been described in PES, associated with a chronic or intermittent altered intracranial pressure: the nightly PRL increment is reduced or completely lacked in patients with intracranial hypertension, even just during the REM phase (47, 48).

Rarely, pituitary hypersecretion condition was described in patients with PES associated to ectopic GH- and ACTH-secreting pituitary adenomas (49, 50), located within the midline intersphenoidal septum.

**Prolactin and dopaminergic and serotonin tone**

Endocrine disturbances can also arise from a neurotransmitter derangement, partly related to CSF...
dynamics and possible immune system reactions. These factors highlight a complex network of primary and secondary effects resulting from the initial anatomic alteration.

As PRL response to dynamic tests is altered in patients with increased CSF pressure, it has been hypothesized that this neuroanatomic finding can influence neuronal dopamine reuptake. In fact, intracranial hypertension interferes with dopamine reuptake, strengthening dopamine’s action at the pituitary level and lowering PRL’s reaction to nomifensine, an indirect dopaminergic agonist (51).

In PES with normal PRL values, for the increased dopaminergic tone, the average peak response to the single TRH and MCP test is not significantly different from that in normal subjects, although there is a trend of higher and more prolonged PRL release and although the PRL percent increment, with respect to basal levels, is often inferior as compared to normal subjects. Moreover, an inverse correlation between basal PRL levels and the post-MCP administration peak increment occurred (52).

In PES with quite high PRL value, laboratory differential diagnosis with PRL-secreting pituitary adenoma represents a great challenge, and pituitary neuroimaging plays a crucial and central role. In fact, an increased central dopaminergic activity with respect to TSH secretion is characteristic of prolactinomas and, when a reaction to TSH and MCP is not present, it is possible to exclude a PRL-secreting pituitary adenoma (53). At least, in pre- and post-menopausal PES-affected patients, PRL dynamics differ, as estrogen-mediated dopamine activation is presumably of a lesser entity than in post-menopausal women. Consequently, in post-menopausal PES-affected patients, PRL response to TRH is often greater that in normal subjects and, in premenopausal PES patients, PRL response to TRH is similar to that in normal women (54).

In young fertile women affected by PES with normal PRL levels, increase of the highest nightly value and re-establish of PRL’s circadian rhythm were observed in patients on treatment with tryptophan, suggesting an alteration of the serotonergic system, which in physiological condition stimulates PRL secretion through central mechanisms (55).

In conclusion, multiple factors can influence PRL dynamic tests in PES, as intracranial pressure, integrity of pituitary stalk, basal PRL value and gonadal status.

**Neurological and ophtalmological picture**

Neurological and ophtalmological signs in PES syndrome are predominantly due to the presence of increased intracranial pressure: values from 14 to 24 mm Hg were insufficient to provoke a clear instance of intracranial hypertension but sufficient to maintain the neurological symptomatology of PES syndrome, such as headache and visual disturbances.

In fact, around 84–88% of PES syndrome cases are affected by headache, typically described as lateral, persistent and datable from years (3, 8). In a lower percentage of cases (around 20%), headache is accompanied by symptoms of intracranial hypertension as papilledema and visual disturbances (3, 8). Neurological disturbances such as dizziness, syncope, cranial nerve disorders, convulsion or depression occurred in around 40% of patients (3). Rarely, CSF rhinorrhea may occur in combination with the empty sella syndrome, increasing the risk of retrograde meningitis.

Ophthalmological picture also includes worsening of visual acuity (13–37%), blurred vision (29%), diplopia (2%), defect in oculomotor nerve (1%) and optical neuritis (1%) (3, 8).

**Diagnosis**

**Imaging studies**

ES can be confirmed through magnetic resonance (MR) study of the sellar and suprasellar regions and with computed tomography (CT), in selected patients with absolute contraindication to the MR. Typical finding of ES (56), both in CT and MR, are intra-sellar CSF filling in continuity with overlying subarachnoid spaces, residual pituitary gland, with a semi-lunate morphology, flattened against the sellar floor and, often, enlarged bony sella (Fig. 2). Pituitary stalk is usually thinned and located on midline. In rare cases, optic chiasma, anterior 3rd ventricle can herniate into the sella. Instead, if intra-sellar CSF herniation is asymmetric, pituitary stalk can be tilted to a site. Sagittal and coronal T1-weighted (T1W) contrast-enhanced images and coronal T2-weighted (T2W) images are strongly recommended for an accurate MR study of ES. T1W and T2W images particularly show a fluid signal within the sella that looks exactly like CSF. On FLAIR sequences, intra-sellar fluid completely suppresses and it presents without restriction in DWI sequences. After contrast,
T1W images evidence normal enhancement of residual pituitary gland and stalk, without any abnormalities. In SES, T1W images before and after contrast injection can prove stalk and pituitary remnants scarred or distorted and adhered to a side or to the bottom of sella turcica (56) (Fig. 3). Asymmetry and erosion of sellar floor can be suggestive of SES (as for previous pituitary neoplasia) (8). MR imaging can focalize also indirect signs of intracranial hypertension (Fig. 4), such as flattening of the posterior sclera, prominent subarachnoid spaces along the optic nerves, vertical tortuosity of the optic nerve sheath complex, protrusion or enhancement of the prelaminar optic nerve (57) and nerve sheath volumes >201.30 mm³ with an hypophysis volume <611.21 mm³ (58).

**Endocrinological assessment**

As hormonal alterations caused by the empty sella syndrome is not clear-cut, an accurate hormone diagnosis is advocated. Therefore, in all patients having an empty sella, basal pituitary hormonal dosage has to be prescribed and, if indicated, dynamic tests are also suggested for identifying hormonal deficit, particularly GHD and secondary hypoadrenalism.

**Ophthalmological assessment**

In the later years, ophthalmic echography has taken up a primary role in the diagnosis of endocranial hypertension, as it is brief, non-invasive, extremely specific and able to provide an indirect evaluation through the observation of the optic nerves’ morphology and the perioptic subarachnoid spaces. The correlation between intracranial CSF dynamic parameters and optic nerve diameters was well established: optic nerve diameters are correlated by a direct, biphasic, positive relation with diastolic intracranial pressure and by a direct relation with the intracranial absorptive reserve (59). Moreover, optic nerve diameters rapidly change in response to variation of intracranial pressure (59). Consequently, the safety, low cost and, above all, the patient’s tranquillity, render ophthalmic echography the chosen methodology both in the initial screening and in the follow-up of PES syndrome. Moreover, in cases of ophthalmic echography suggestive of intracranial hypertension, ophthalmological evaluation has to be

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**Figure 2**

Primary empty sella MR study: (A and B) Sagittal and coronal post-contrast T1w images show enlarged sella with marked thinning of the pituitary gland and of the stalk. The latter shows normal enhancement after contrast injection; (C) Coronal T2w image confirms sella partially filled with arachnoid-lined CSF collection.

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**Figure 3**

Secondary empty sella in patient affected by primary autoimmune hypophysitis MR study: (A and B) Sagittal and coronal post-contrast T1w images show increased volume of the whole pituitary gland and pituitary stalk related to inflammatory changes. (C and D) Sagittal and coronal post-contrast T1w images obtained two years later, show complete response to the therapy with marked thinning of pituitary gland and stalk; the latter is slightly located to the left.
completed with computerized field view and visual evoked potential, to detect a possible neurological damage. All these examinations should be performed at PES diagnosis and during follow-up, according to the clinical features, for surveillance and for evaluating possible treatment efficacy.

**Differential diagnosis**

Empty sella has to be distinguished from other pituitary abnormalities or cystic lesions, as arachnoid and epidermoid cysts and congenital pituitary anomalies. Suprasellar arachnoid cyst may in fact herniate into bony sella, which may appear enlarged or eroded. The 3rd ventricle or the optic chiasm may be displaced by CSF-containing mass, whose walls can be easily recognizable on thin-section imaging (56). Instead, intrasellar epidermoid cysts are very rare, as usually are localized off midline, with an extension from cerebellopontine angle epidermoid (56). Moreover, some congenital pituitary abnormalities can mimic a partial empty sella, as the persistence of the embryonal infundibular recess of the 3rd ventricle, the presence of a pituitary stalk duplication or the presence of an ectopic posterior pituitary ‘bright spot’, also characterized by small pituitary gland, short infundibular stalk, often small bony sella (56).

Therefore, empty sella syndrome requires a multidisciplinary diagnosis and management with the integration of endocrine, neurologic and ophthalmologic experts (Fig. 5).

**Figure 4**

Primary empty sella associated with intracranial hypertension MR study: (A and B) Sagittal and coronal post-contrast T1w images show marked and slightly asymmetric thinning of the central portion of the pituitary gland. The stalk is very thin, tilted backward and shows normal enhancement after contrast injection. (C) Coronal fat-saturated T2w image shows prominent subarachnoid spaces along the optic nerves.

**Figure 5**

Flow-chart of the diagnosis and management of empty sella syndrome according to the symptoms referred by the patients.
Treatment strategies

Hypopituitarism

Replacement hormone therapy in PES syndrome must be assessed for every single hormone and administered according to the appropriate temporal sequence. In the presence of multiple pituitary hormone deficiencies, it is recommended that hormonal replacement treatment starts with hydrocortisone, followed by levothyroxine. Hormonal replacement treatment with sexual hormones should be introduced when the patient’s conditions are stabilized. The therapeutic plan should be completed with the administration of rhGH, when indicated and in patients not affected by intracranial hypertension. Hyperprolactinemia should be treated with dopamine-agonist drugs, as patients can improve biochemically and clinically (8).

Intracranial hypertension

Intracranial hypertension has always to be treated. In overweight or obese patients, the first suggested therapeutic approach is the weight loss, which can improve neurological symptoms (60) through personalized hypocaloric diet or bariatric surgery. In fact, grade of papilledema and percentage of weight loss are positively correlated (61). However, in patients affected by hypopituitarism, an accurate evaluation of the risk of a malabsorption syndrome has to be performed to assure the patients an optimal management of hormonal replacement therapies. Moreover, in PES syndrome affected patients, with signs or symptoms of intracranial hypertension, the best therapy is based on the administration of osmotic diuretics per os, such as acetazolamide (acetazolamide, Diamox tab 250mg, with a dose range of 250–500mg/day) or escin (Reparil tab 40mg, with a dose range of 100–250mg/day), which can improve neurological manifestation, as showed in other intracranial hypertension condition (62). According to recent evidence, in obese patients (60) with intracranial hypertension, bariatric surgery should represent the first surgery procedure, if not contraindicated and after the failure of treatment with personalized hypocaloric diet or in cases resistant to medical treatment. Lumboperitoneal shunt is generally reserved for very selected patients with severe visual impairment (63) or in patients with progressive visual loss despite other medical or bariatric surgery intervention (63). The appearance of rhinorhea and the worsening of the visual alterations makes peritoneal-ventricular surgery necessary, in order to avoid serious intracranial hypertension complications such as progressive reduction of visual acuity, campimeter deficits, papilledema and optical atrophy (63). However, treatment of CSF rhinorrhea remains a challenge and requires a safe and effective therapeutic strategy. Direct surgical repair of the skull defect should be performed in cases with normal CSF pressure and dynamics, instead CSF drainage should be performed in cases with abnormal CSF pressure and dynamics.

Therefore, empty sella syndrome requires a multidisciplinary therapeutic approach and follow-up with the integration of endocrine, neurologic and ophthalmologic experts (Fig. 6).

Follow-up

Empty sella represents a very heterogeneous condition, ranged from a merely occasional neuroradiological

Figure 6
Flow-chart of the multidisciplinar management and follow-up of PES syndrome.
finding without any clinical involvement, to the empty sella syndrome, characterized by the occurrence of endocrine, ophthalmological and neurological symptoms or a combination of these. Consequently, management of these patients should be modulated according to the clinical context.

Patients who had empty sella, without any clinical manifestation or abnormalities at the time of diagnosis, because of the theoretical risk of PES syndrome occurrence, should be re-evaluated with a larger follow-up (after 24–36 months) to early recognize occurrence of endocrine or ophthalmological alteration, if there are no clinical indications before. In particular, neuroradiological study should be able to recognize early the possible signs of IIH (8). If progression is not observed, additional control evaluation could be even less frequent and limited to those patients requiring it clinically (8).

In PES syndrome cases, patients medically treated for endocrine, ophthalmological or neurological should be re-evaluated according to appropriate well-established guidelines and at least twice in the year. Patients treated surgically for IIH should also be re-evaluated for assessing long-term results and side effects at least twice in the year after surgery (8).

In SES cases, all patients should be evaluated according diagnosis and management of hypopituitarism and according to the etiology of SES (8).

**Conclusion**

ES, in the majority of cases, is only a neuroradiological finding, without any clinical implication. Instead, PES syndrome should be distinguished and properly managed, as it represents a peculiar clinical entity, characterized by heterogeneity both in clinical manifestations and in hormonal alterations, sometime reaching severe extremes. For a proper diagnosis, management and follow-up of PES syndrome a multidisciplinary approach with the integration of endocrine, neurologic and ophthalmologic experts is strongly advocated.

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**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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