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Pituitary Stalk Enlargement in Adults

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Keywords
Enlarged pituitary stalk · Diabetes insipidus · Hypopituitarism · Diagnostic approach

Abstract
Pathologies involving the pituitary stalk (PS) are generally revealed by the presence of diabetes insipidus. The availability of MRI provides a major diagnostic contribution by enabling the visualization of the site of the culprit lesion, especially when it is small. However, when only an enlarged PS is found, the etiological workup may be difficult, particularly because the biopsy of the stalk is difficult, harmful and often not contributive. The pathological proof of the etiology thus needs to be obtained indirectly. The aim of this article was to provide an accurate review of the literature about PS enlargement in adults describing the differences between the numerous etiologies involved and consequent different diagnostic approaches. The etiological diagnostic procedure begins with the search for possible other lesions suggestive of histiocytosis, sarcoidosis, tuberculosis or other etiologies elsewhere in the body that could be more easily biopsied. We usually perform neck, thorax, abdomen, and pelvis CT scan; positron emission tomography scan; bone scan; or other imaging methods when we suspect generalized lesions. Measurement of serum markers such as human chorionic gonadotropin, alpha-fetoprotein, angiotensin converting enzyme, and IgG4 may also be helpful. Obviously, in the presence of an underlying carcinoma (particularly breast or bronchopulmonary), one must first consider a metastasis located in the PS. In the case of an isolated PS enlargement, simple monitoring, without histological proof, can be proposed (by repeating MRI at 3–6 months) with the hypothesis of a germinoma (particularly in a teenager or a young adult) that, by increasing in size, necessitates a biopsy. In contrast, a spontaneous diminution of the lesion is suggestive of infundibulo-neurohypophysitis. We prefer not to initiate steroid therapy to monitor the spontaneous course when a watch-and-see attitude is preferred. However, in many cases, the etiological diagnosis remains uncertain, requiring either close monitoring of the lesion or, in exceptional situations, trying to obtain definitive pathological evidence by a biopsy, which, unfortunately, is in most cases performed by the transcranial route. If a simple surveillance is chosen, it has to be very prolonged (annual surveillance). Indeed, progression of histiocytosis or germinoma may be delayed.

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Introduction

Lesions of the pituitary stalk (PS) are relatively rare but often represent a diagnostic challenge for even experienced clinicians. Diabetes insipidus (DI), either isolated or associated with anterior pituitary deficiency, raises the suspicion of PS pathology. Increasing the number of MRI and positron emission tomography (PET) examinations may also lead to the discovery of incidental PS lesions, either asymptomatic or before the occurrence of overt symptoms [1–3].

Pathological conditions involving the PS are generally attributed to 3 etiological groups: neoplasia, inflammatory/infectious diseases and congenital abnormalities (Table 1). In this review, we describe the differences between these etiologies and consequent diagnostic approaches.

Anatomy

The PS contains neuronal axons elongating from the supraoptic and paraventricular nuclei, along which secretory granules of oxytocin and vasopressin migrate to be stored in the posterior lobe of the pituitary (neurohypophysis) before their release into the bloodstream when necessary. Along the PS, portal veins supply the anterior lobe of the pituitary with hypothalamic regulatory hormones. The anterior pituitary has 3 parts, namely, *pars distalis* (the largest part), *pars intermedia* and *pars tuberalis*, which extend up and closely encircle the PS. In the *pars tuberalis,* TSH, LH, FSH and ACTH staining cells have been described. However, these TSH-stained cells lack T3 and TRH receptors but express melatonin MT1 receptors, which are involved in the photoperiodic stimuli pathways. Thus, they can be under the influence of melatonin secreted from the pineal gland [4, 5].

MRI Imaging

The normal PS appears as a funnel-like median structure connecting, obliquely, the median eminence of the hypothalamus to the pituitary gland. The superior part of the stalk is larger than the inferior part, and the tapering of the stalk is smooth without abrupt changes in size or contour. Careful examination of the images is mandatory. Indeed, the infundibular recess can vary greatly in shape and size, and the degree of its extension inferiorly along the PS may contribute to the size and contour of the PS in its proximal part that can mimic stalk thickening [6]. Knowledge of the normal size of the infundibular recess is important for the assessment of pituitary infundibular lesions. On oblique-axial images obtained with 1.5 T MRI, normal measurement of the PS transverse diameter is (mean ± SD) 3.25 ± 0.56 mm (range 1.56–4.58 mm) at the level of the optic chiasm and 1.91 ± 0.4 mm (1.04–2.93 mm) at its insertion on the pituitary gland; on 3 T MRI, these diameters are 3.35 ± 0.44 mm (2.39–4.21) and 2.16 ± 0.37 mm (1.56–3.04) respectively [7, 8]. Standard MRI T1-weighted (T1W) and T2W sequences use 2–3-mm-thick images. The MRI T2 weighted *driven equilibrium* (fast recovery, DRIVE) technique is a more precise method that yields a submillimetric cut thickness. With this technique, the PS diameter at the proximal level of the optic chiasm is 2.37 ± 0.61 mm and, at its insertion on the pituitary gland, it is 1.28 ± 0.52 mm [9].

MRI imaging should include, apart from noncontrast T1W and T2W sequences, contrast-enhanced T1W sequences. At least one sequence of the entire brain is also greatly advised. At least a fluid attenuation inversion recovery, a postcontrast T1 and a diffusion-weighted imaging sequence on the axial plane should be acquired to rule out additional brain abnormalities. In cases of suspected or confirmed germinoma, a spine MRI should be considered to exclude tumor dissemination [10].

The posterior pituitary bright spot (PPBS), where vasopressin is stored, is visible in more than 95% of healthy subjects [11]. In the case of central DI, the PPBS disappears [12]. However, to accurately determine whether the posterior lobe is visible, it may be necessary to use the axial T1W and fat saturation T1W sagittal sequences. Particular imaging characteristics, when specific, are mentioned with each etiology.

Positron Emission Tomography

PET/CT examination of the pituitary and PS lesions can provide valuable information for the differential diagnosis. Nevertheless, one must remember that common pituitary adenoma may demonstrate ^{18}F-FDG uptake. Mostly available ^{18}F-FDG PET/CT has shown a correlation between pituitary adenoma size and SUVmax. In patients with malignancy treated by immunotherapy, hypophysitis can be identified. In cases of suspected pituitary Langerhans cell histiocytosis (LCH), it unravels the spread of this multisystemic disease and shows potential sites that are more accessible for skin or bone biopsy. Rathke cleft cysts (RCCs) usually do not show ^{18}F-FDG uptake. Other novel tracers, such as ^{68}Ga-DOTA-TATE, ^{11}C-methionine, and ^{8}F-choline, have also shown promising results for specific diagnostic questions [13].

Table 1. Etiological groups in various series of isolated PS lesions in adults

Author, *n*, year	Reference	Neoplastic	Inflammatory	Congenital	Unknown
Doknic, *n* = 53, 2018**	[69]	9/53	9/53	25/53***	10/53
Catford, *n* = 75, 2016	[32]	19/75	51/75	3/75	2/75
Turcu, *n* = 152*, 2013	[3]	49/152	30/152	13/152	60/152
Hamilton, *n* = 44, 2007	[2]	16/44	19/44	9/44	Not included
Zhou, *n* = 230, 2019	[63]	45/230	35/230	15/230	135/230
Sbardela, *n* = 26, 2016	[66]	3/26	8/26	4/26	11/26
Devuyst, *n* = 38, 2020	[64]	11/38	27/38	0/38	0/38
Mean		24%	28%	11%	37%

* 76%, ** 89% of lesions with isolated PS involvement, 2 children in the group, *** 84% of PS interruption syndrome cases. PS, pituitary stalk.

Table 2. Clinical characteristics of most PS lesions

		Clinical features leading to the diagnosis
Neoplastic		
Local	Germinal cell tumors	hCG, AFP, ALP in serum and CSF in case of radiological suspicion, children and young adults, synchronous pineal germinoma occurrence possible
	Craniopharyngioma	Typical imaging features, calcifications
	Astrocytoma, glioblastoma	Both can present as CSF disseminated disease
	Pituitary adenoma	Hormonal hypersecretion is possible, no DI (except in case of apoplexy)
	Pituicytoma	Middle aged men, usually no pituitary involvement, not described in children
	Lymphoma primary in CNS	CSF cytology, flow cytometry, immunohistochemistry and PCR
	Meningioma	Usually isointense to grey matter on both T1W and T2W imaging, highly enhancing on both MRI and CT, dural tail in 60–72%
Metastases	Breast cancer	Mammography/ultrasound with tumor biopsy
	Lung cancer	Thorax CT, bronchoscopy
	Renal carcinoma	Primary tumour
	Nasopharyngeal carcinoma	Primary tumor
	Prostate carcinoma	Primary tumor
	Hemangioblastoma	May be associated with polycytemia, pancreatic cysts or Von Hippel-Lindau disease
	Lymphoma systemic	Lymphadenopathy
	Leukemia	Bone marrow examination
	Metastasis of unknown origin	
Inflammatory	Neurosarcoidosis	Fatigue, weight loss, fever, persistent cough, skin changes, eye lesions, peripheral lymphadenopathy
	Langerhans cell histiocytosis	Multisystem disease, bones, lymphadenopathy, skin changes, thyroiditis, other autoimmunity
	Hypophysitis	Pregnancy, abortion/immunotherapy, most frequent ACTH and TSH deficiency in primary hypophysitis, limited value of pituitary antibodies, symmetric pituitary enlargement on MRI

Table 2 (continued)

		Clinical features leading to the diagnosis
	Erdheim-chester disease	Symptoms similar with LCH, symmetric diaphyseal and metaphyseal osteosclerosis in the legs, perinephric fat infiltration
	Tuberculosis	Quantiferron assay, CSF microscopy, PCR and culture
	Whipple's disease	Diarrhea, abdominal, joint pain, malabsorbtion, confirmation by duodenal detection of *Tropheryma whipplei*
	Xanthoma disseminatum	Normolipemic disseminated xanthomatosis most on the flexural and intertriginous surfaces, often with DI
	Lupus cerebritis	Neuropsychiatric symptoms in patients with systemic lupus erythematosus
	Bacterial/mycotic abscess	MRI image, fever, inflammation markers, CSF microscopy and culture
	Behçet disease	Mucocutaneus oral, genital or other lesions, visual impairment, arthritis
Congenital	Ectopic neurohypophysis	High signal nodule in the area of the infundibular recess of the third ventricle or along the pathway of a thin PS connecting the hypothalamus to the pituitary gland
	Rathke cleft cyst	In the midline, non-enhancing, round, well-demarcated lesions with homogeneously hyperintense T1W signal and hypointense T2W signal
	Normal variant	
	PS interruption syndrome	Thin PS in most cases, permanent childhood onset or with age progressive anterior pituitary deficiency, GH deficiency being most frequent, DI rather rare

PS, pituitary stalk; hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; ALP, alkaline phosphatase; PCR, polymerase chain reaction; T1W, T1-weighted; T2W, T2-weighted; DI, diabetes insipidus.

Etiologies

The PS area contains a wide spectrum of different cell types with many signaling pathways. Therefore, pathologies arising from the stalk area are also very heterogeneous. Specific features of each condition are mentioned in the following paragraphs and in Table 2.

Tumors

Germinal Cell Tumors (GCT)

Primary central nervous system (CNS) GCT account for 0.5% of all primary brain and CNS tumors, with approximately 90% of the cases occurring before the age of 20 years [14]. GCT represents a group of tumors originating from germinal cells that migrate into the CNS during fetal development. These tumors arise predominantly in children and young adults (in the second and third decades), where they are the most frequent tumoral cause of DI [1]. Germinomas account for 60–80% of GCTs in the hypothalamo-pituitary region, whereas choriocarcinomas, teratomas, mixed tumors and other GCTs are less frequent [14].

Symptoms can be variable from growth failure, precocious or delayed puberty, hypopituitarism, DI, or neurological symptoms [15, 16].

On MRI (Fig. 1), GCTs in the suprasellar region may be difficult to differentiate from other lesions [17]. Cerebrospinal fluid metastatic seeding with leptomeningeal and subependymal enhancement on MRI has been documented in some cases, so a spine MRI should also be considered for helping the diagnosis [18]. Bifocal localization of suprasellar and pineal tumors without further dissemination is highly suggestive of a germinoma [15, 19]. Additionally, involvement of the basal ganglia raises the suspicion of germinoma [10].

The serum tumor markers alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) and placental alkaline phosphatase (ALP) are elevated in some GCTs, mostly in choriocarcinomas. Isolated increased levels of AFP are characteristic of a yolk sac tumor, whereas that

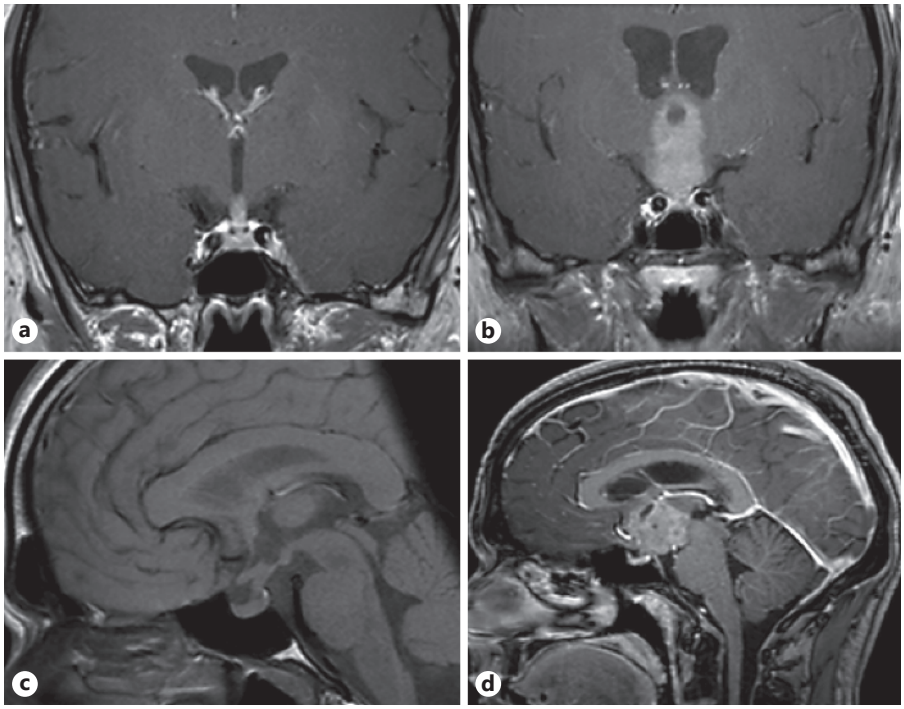

Fig. 1. Germinoma in a young male patient, (**a**, **c**) at presentation, (**b**, **d**) 6 months later.

of hCG strongly suggests the presence of a choriocarcinoma. At high levels, these markers are detected in serum, but measurement in cerebrospinal fluid (CSF) is more sensitive and reliable [20].

Pure germinomas are less invasive and better respond to radiotherapy than other GCTs and mixed types [17].

Craniopharyngiomas

Craniopharyngiomas represent 2–5% of all primary intracranial neoplasms. They probably arise from neoplastic transformation of embryonic squamous cell rests of the involuted craniopharyngeal duct connecting the stomodeal ectoderm with Rathke's pouch [21, 22]. The incidence of these tumors is bimodal, which is reflected by the distinct histological characteristics. The adamantinomatous type is found in 95% of cases in children, and the papillary type is preponderant at adult age. Primary PS craniopharyngioma is unusual but has been reported in case series. The multicomponent features of the lesion with cystic, solid and calcified parts (the latter being only visible on CT scan) help to make the diagnosis on imaging, when present. The therapeutic approach is usually surgical with potential adjuvant radiotherapy [23].

Pituitary Adenomas

Isolated stalk enlargement related to the presence of a pituitary adenoma is rare, since these tumors generally arise in the adenohypophysis and may secondarily develop in the suprasella. Out of 516 patients with Cushing's disease, 4 microadenomas originated in and were confined to the stalk. In all of them, remission was achieved by endoscopic operation [24]. Elevated levels of pituitary hormones are suggestive of an ectopic pituitary adenoma.

CNS Lymphomas

CNS lymphomas may arise primarily or be secondary to another lesion elsewhere in the body [25]. Few cases of primary sellar lymphomas have been reported. Lymphoma may initially be localized in the PS [26]. In most of them, the diagnosis was made at biopsy or after removal of the lesion. CSF cytology, flow cytometry, immunohistochemistry and polymerase chain reaction may help to achieve the diagnosis [27–32].

Astrocytomas

Astrocytoma is a tumor originating from glial cells. It is very rare in this location. In a case report, a low-grade astrocytoma was uncovered upon a central DI. After MRI surveillance, a stereotactic biopsy allowed histological diagnosis and then fractionated radiotherapy [33].

Pituicytomas

These benign tumors arise from neurohypophyseal glial cells. Pituicytomas mostly occur in middle-aged men

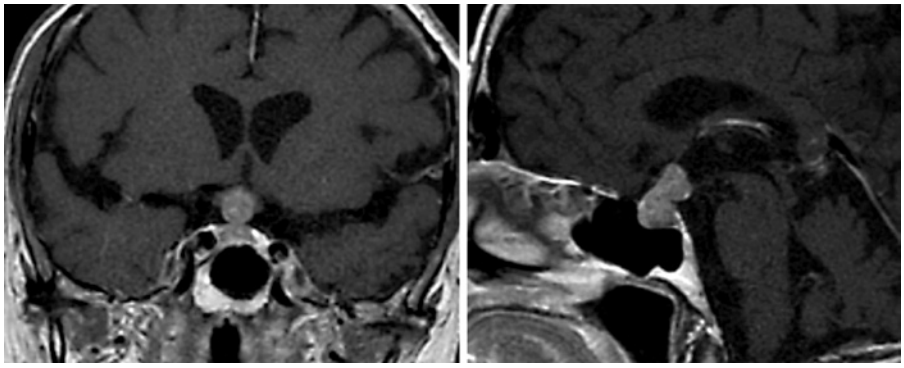

Fig. 2. Pulmonary adenocarcinoma metastasis.

in the third to fifth decade. None have been described in children. They are localized to the PS and posterior gland and frequently grow into the suprasellar cistern, eventually compressing the optic nerves and hypothalamus. Sellar expansion is uncommon and so may help to differentiate them from adenomas [2]. They are usually slowly growing and highly vascularized, which can complicate surgical resection. The radiological finding is nonspecific, and diagnosis is mostly made upon biopsy [34]. Total resection is usually curative; thus, no adjuvant chemotherapy or radiation is required [2].

Metastases

Metastatic lesions to the PS region are usually discovered when an MRI is performed in a patient (generally older) who suddenly develops a central DI and who is already known to suffer (or has suffered in the past) from a cancer in another location (Fig. 2). The most frequent primary sites are breast cancer, lung cancer and lymphomas [3, 16, 35].

Inflammatory/Infectious/Multisystemic Diseases

Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown cause characterized by the development of granulomas in various organs, mainly the lungs and lymphatic system. The pathophysiology is still not clear, but many studies suggest genetic susceptibility to exaggerated immune responses to unidentified antigens [36].

Involvement of the CNS in sarcoidosis is infrequent (in 5% of cases), but when it occurs, the hypothalamo-pituitary area is often inflicted [37, 38]. Sarcoidosis is probably the most frequent cause of PS enlargement in adults [3, 32]. Both hypopituitarism of variable degree and DI are frequent in hypothalamo-pituitary sarcoidosis localization. MRI findings of other neurosarcoidosis lesions are found in half of cases [39]. In more than 95% of cases, multiorgan involvement (lungs, mediastinal lymphadenopathy) is present [38]. Diagnosis is based on histological confirmation of granulomas, most commonly from biopsy, transbronchial or lymphatic nodes, clinical and radiological presentation and exclusion of other granulomatous diseases such as tuberculosis.

To achieve this, a thorough history of symptoms followed by a whole-body clinical examination is essential. General symptoms of sarcoidosis are fatigue, weight loss, and fever, which may be associated with more specific symptoms, such as persistent cough, skin changes (papules, nodules, subcutaneous infiltrates, erythema nodosum, lupus pernio), eye lesions (uveitis, retinal changes, conjunctival nodules), and peripheral lymphadenopathy.

Elevation of serum angiotensin converting enzyme has variable sensitivity 24–76% according to previous studies [40]. Analysis of bronchoalveolar lavage, for example, increased CD4/CD8 lymphocyte ratio, is not specific for sarcoidosis. The interleukin-2 receptor and neopterin predict ^{18}F-FDG PET uptake, but they do not have 100% sensitivity [41]. Hypercalcemia and hypercalciuria in sarcoidosis are thought to result from the endogenous overproduction of an active vitamin D metabolite, but the prevalence of hypercalcemia in sarcoidosis is 5–10% [42, 43]. Nonspecific elevation of liver enzymes occurs in 20–30% of patients [36].

CSF abnormalities found in neurosarcoidosis are usually nonspecific and include mild pleocytosis, high protein content, and, sometimes, slightly low glucose concentrations. Determination of the angiotensin converting enzyme concentration in the CSF is not specific but seems to be especially useful in the monitoring of disease activity and treatment response [38].

The MRI image of neurosarcoidosis is sensitive for detection and localization but not specific for sarcoidosis, as its MRI presentation is variable (Fig. 3). The lesion is usually strongly enhanced after contrast agent injection [39].

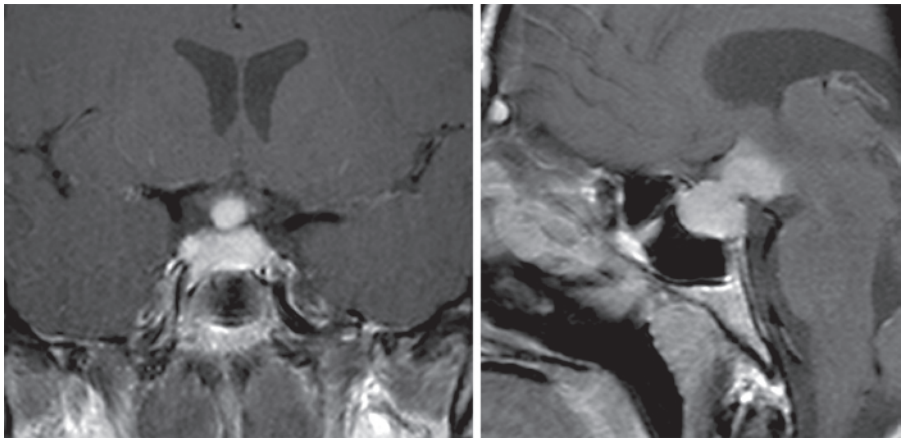

Fig. 3. Sarcoidosis lesion of the PS and of the pituitary.

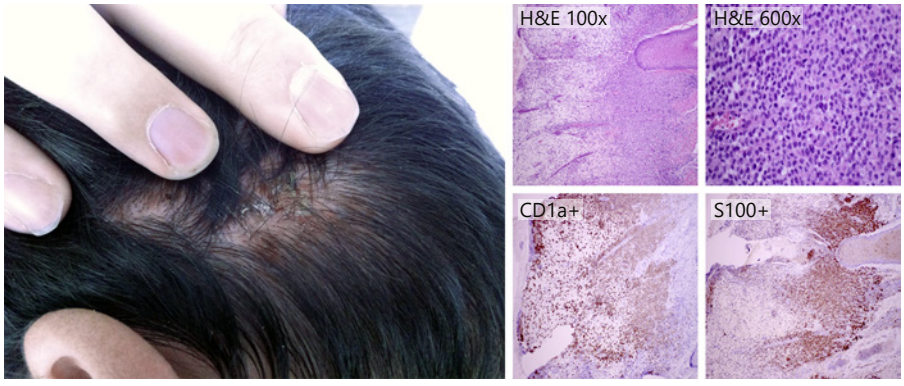

Fig. 4. Langerhans cell histiocytosis scalp lesion with immunohistological staining. H&E, hematoxylin and eosin.

Chest X-ray is abnormal in 90% of cases of sarcoidosis. Thoracic CT, although not always needed, helps when there is a difficult diagnosis or complications, particularly pulmonary fibrosis. In the case of hypothalamo-pituitary involvement, a whole-body gallium or FDG-PET scan can show other lesions that are more accessible for biopsy [38].

Langerhans Cell Histiocytosis

Histiocytic disorders are characterized by the accumulation of histiocytes, an old term for tissue resident macrophages and dendritic cells. LCH, the most frequent histiocytosis, has been thought to arise from epidermal dendritic cells called Langerhans cells. LCH has variable presentation, ranging from a single indolent lesion to explosive multisystemic disease [44]. Recent research has shown that LCH and other histiocytic disorders etiologically classified among inflammatory disorders share some characteristics of neoplasia, such as *BRAF* V600E somatic mutation, but the pathogenesis is still unclear [45].

Pituitary involvement with DI and variable hypopituitarism is the most frequent CNS localization, found in 5–50% of patients with LCH [46]. Two different phenotypes are usually described in children and adults. In adults, bone, lung, skin and DI predominate, whereas in children, liver, spleen, lymph node and bone marrow involvement prevails [47]. The diagnosis of LCH should be based on histologic examination, which is most frequently made from bone, lung or skin lesions [48]. Langerhans cells stain positively with CD1a and Langerin (CD 207) [45, 49].

Patients with LCH are often asymptomatic or present mild symptoms such as fatigue, generalized weakness, weight loss, night sweats, nausea, pruritus and fever. Careful history can reveal thyroid disease (LCH infiltration with underlying thyroiditis), DI, lung cysts, pneumothorax, bone lesions, smoking and family history of autoimmune disease [50].

On clinical examination, most common bone lesions in children are located in the skull and are either asymptomatic or painful, often with reactive soft tissue mass.

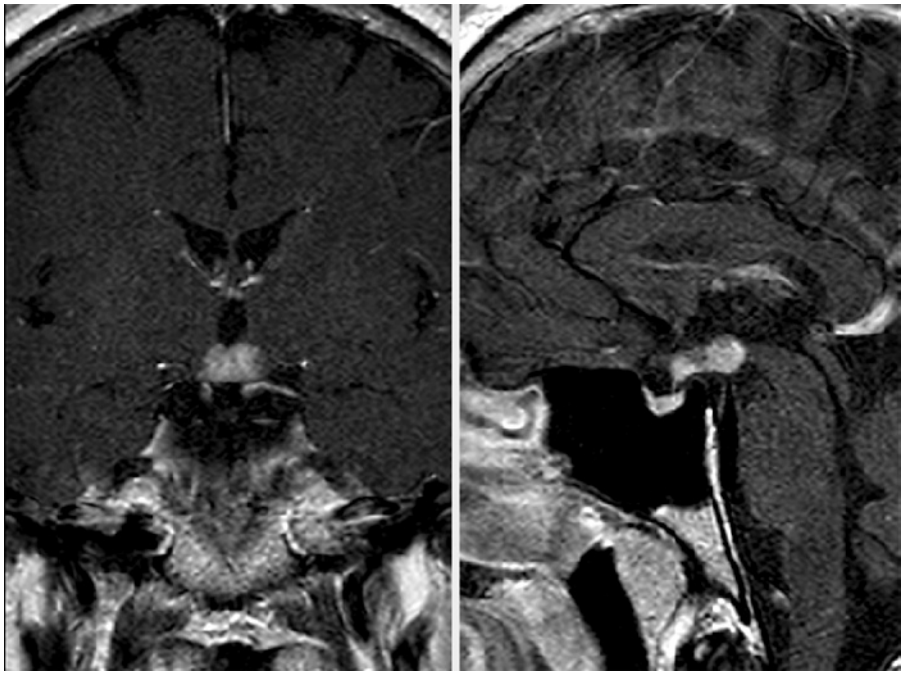

Fig. 5. Langerhans cell histiocytosis, T1-W postgadolinium MRI.

Other frequent locations are the ribs, humerus, vertebra, and periorbital infiltrates.

Skin lesions include seborrheic involvement of the scalp (Fig. 4), which can be easily misdiagnosed without LCH suspicion. Crusted dermal areas of the trunk, perigenital area, and behind the ears (Fig. 4) healing with depigmentation; gingival hypertrophy and oral ulcers; or lymphadenopathy can occur. Symptoms from pulmonary involvement are often nonspecific, especially in smokers [47].

Laboratory tests include standard biochemistry (including TSH, fT4), blood count, basic coagulation parameters and urine analysis. CSF levels of neurofilament protein light chain, glial fibrillary acid protein and total tau protein seem to be elevated in CNS-LCH, but this finding needs to be validated in further studies [51].

MRI images (including postcontrast enhanced sequences) of the hypothalamo-pituitary lesion lack specificity for LCH (Fig. 5), but a combination of changes in the cerebellum, basal ganglia, and/or pons, with characteristic patterns seen on MRI called "radiological neurodegeneration," can be found [46]. The infundibulum was found to be enlarged in 71% of patients with LCH presenting with DI at the time of diagnosis [45, 52].

Skeletal survey can be performed by multiple X-ray images and CT scans, but FDG-PET/CT offers greater accuracy and allows a precise localization of lesions that are more easily accessible for biopsy than the PS [53].

Erdheim-Chester Disease

Erdheim-Chester disease is a very rare, non-Langerhans histiocytosis. It shows negative staining by CD 1a and Langerin (CD 207). It shares many clinical symptoms with LCH. Clinical characteristics include nearly always symmetric diaphyseal and metaphyseal osteosclerosis in the legs with or without other skeleton lesions, dense infiltration of perinephric fat, described as a "hairy kidney" in 68% of cases with a possible consequent hydronephrosis, skin xantelasma, perimyocardial infiltrates and periaortic infiltration by pseudoretroperitoneal fibrosis [54].

Infundibulo-Neurohypophysitis

Hypophysitis is a rare inflammatory disease of the pituitary gland. Based on histological findings, it can be divided into lymphocytic, granulomatous, xantomathous, IgG4-related and necrotizing hypophysitis. Anatomical classification comes from radiological (MRI) pictures of the afflicted part: adenohypophysitis, infundibulo-neurohypophysitis (Fig. 6), and panhypophysitis. According to the etiology, hypophysitis is called primary if the inflammation involves only the pituitary gland. Autoimmune etiology is expected in these cases. Primary hypophysitis is considered to be mainly related to pregnancy or postpartum, but this is no longer the case at present [55, 56].

Secondary hypophysitis is believed to be triggered by other focal pituitary processes, such as craniopharyngiomas, germinomas, adenomas, and RCCs.

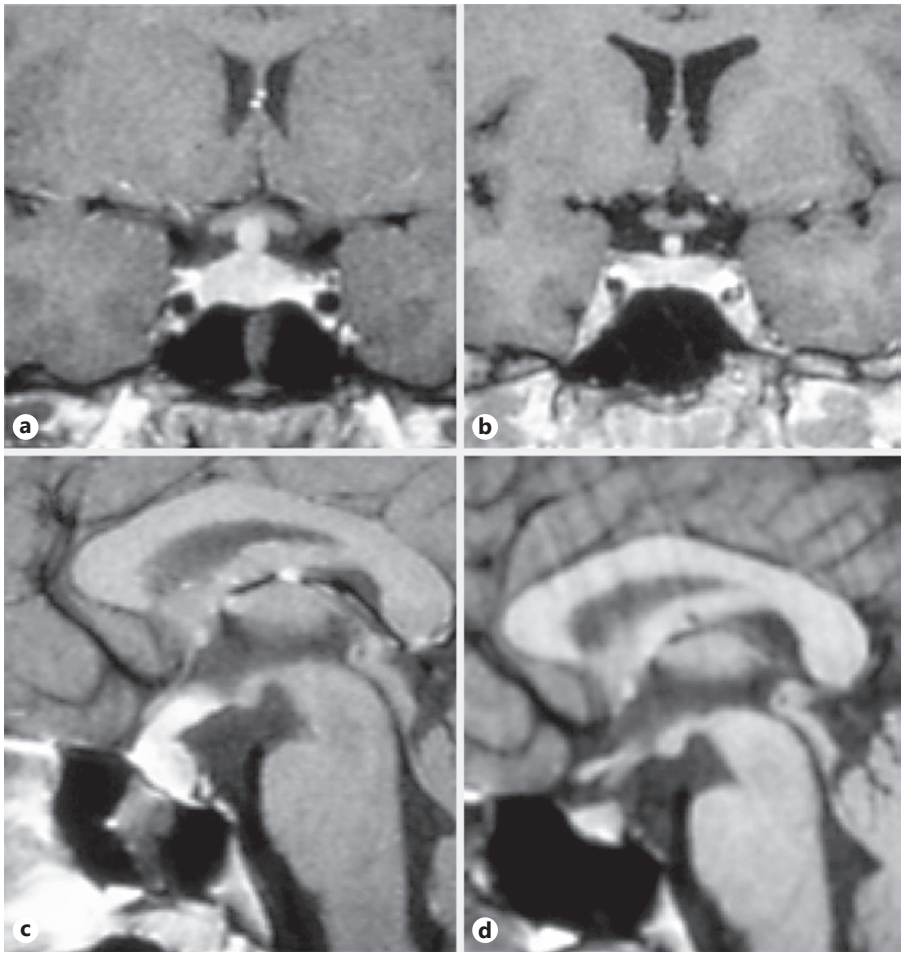

Fig. 6. Lymphocytic infundibulo-neurohypophysitis (**a**, **c**) at presentation, (**b**, **d**) 3 months later showing the spontaneous regression.

With emerging new immunotherapies, such as immune checkpoint inhibitors (CTLA-4, PD-1, PD-1L), interferon-α, and ribavirin, immunotherapy has become the most frequent cause of secondary hypophysitis [57].

Infundibulo-neurohypophysitis usually presents with polyuria and polydipsia resulting from central DI. Hyperprolactinemia as a sign of decreased dopamine inhibition from PS impairment can also be present [58].

The clinical utility of pituitary antibodies in primary hypophysitis is limited due to their low diagnostic sensitivity (64%) and specificity (86%) [59].

On MRI, a PS enlargement is observed, with PPBS missing in most cases associated with DI on T1-weighted sequences [58].

Although biopsy remains the gold standard for diagnosing these disorders, the current standard of practice is biochemical assessment for hormonal deficiencies, exclusion of other diagnoses and watchful imaging surveillance with substitution of pituitary deficiencies [55]. Some authors recommend glucocorticoid or other immunosuppressive therapy in primary hypophysitis where it is not contraindicated [57, 58, 60].

Congenital

In some patients, PS enlargement may be the consequence of a developmental process.

Ectopic Posterior Pituitary

On MRI, ectopic posterior pituitary appears as a bright nodule in T1W sequences before any contrast injection in the area of the infundibular recess of the third ventricle or along the pathway of a thin PS connecting the hypothalamus to the pituitary gland. Ectopic posterior pituitary has become part of the PS interruption syndrome alone or with interrupted stalk and hypo- or aplasia of the anterior lobe, which is associated with a variable degree of hypopituitarism [61].

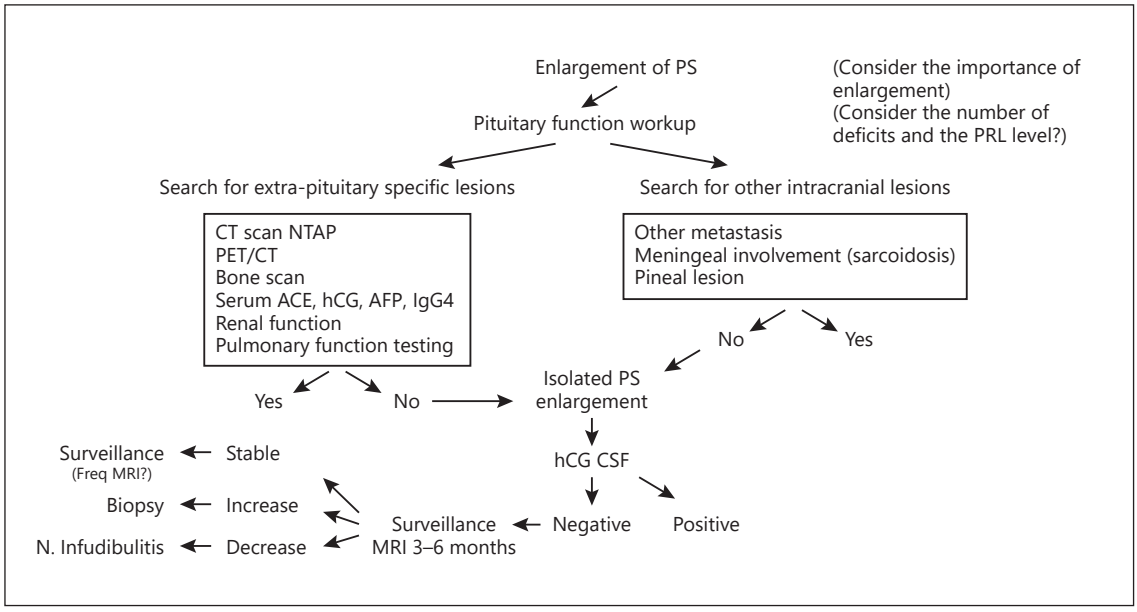

Fig. 7. Proposed pituitary workup scheme in a patient with a PS enlargement. PS, pituitary stalk; PET, positron emission tomography; hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; ACE, angiotensin converting enzyme.

Rathke Cleft Cyst

RCCs are typically intrasellar and asymptomatic but can occasionally present with compressive symptoms and pituitary anterior dysfunction or DI. Suprasellar extension appears in up to one-third of cases. They usually appear as nonenhancing, round, well-demarcated lesions with homogeneously hyperintense T1 signal and hypointense T2 signal, arising in the midline between the anterior and posterior pituitary lobes, but they may be confined to the PS [3, 62].

Diagnostic Approach

Tumors are generally more frequent causes of enlarged PSs in children, whereas inflammatory pathologies prevail in adults (Table 1). In young children and adolescents, a GCT should be questioned first [63]. Specific diagnostic features of most mentioned etiologies are summarized in Table 2.

A proposed diagnostic approach is shown in Figure 7. The first step in all patients presenting with PS process is the evaluation of anterior and posterior pituitary function. Hormonal deficiencies such as DI, central hypocortisolism and central hypothyroidism need to be explored and treated. Data obtained in our cases of DI associated with enlargement of the PS may indicate that tumoral causes of PS enlargement are more prone to be associated with pituitary dysfunctions and increased PRL levels compared with nonneoplastic causes [64]. The potential mass effects (visual field defects, cranial nerve involvement) also need to be evaluated. Whole-body examination searching for potential signs of systemic disease is indicated when DI and enlarged PS are the presenting symptoms/signs. The skin and mucosa need to be cautiously scrutinized (if possible by a dermatologist) to look for any suspected lesion to be biopsied, and bone lesions need to be evaluated by whole-body PET/CT, bone scan, or directed X-rays to find evidence of histiocytic disorders; thorax X-ray and CT scan are useful, particularly in cases of cough, for diagnosis of sarcoidosis; clinical examination and CT scan will help to find any evidence of breast tumor or lymphadenopathy.

Careful history of symptoms, comorbidities, environmental factors, congenital and hereditary disorders, and history of pregnancy are also useful.

Neuroradiologists skilled in pituitary but also cranial imaging are essential for helping the diagnosis. Indeed, LCH can show concomitant cerebellum, basal ganglia, and/or pons lesions, concomitant pineal gland tumor favors the diagnosis of germinoma, sarcoidosis is frequently associated with other intracranial lesions or meningeal involvement, and congenital defects show typical findings on imaging [2]. However, when isolated, it is often

impossible to distinguish between the various causes of enlarged PS. Whole-body PET/CT examination searching for multisystemic diseases can facilitate diagnostic decision making.

Different studies have tried to build diagnostic decision trees based on statistical analysis of the various imaging and hormonal characteristics of patients with enlargement of the PS. In one study, by order of priority, the characteristics that favor inflammatory etiology (vs. tumoral etiology) were (1) lesion confined to the PS without extrasellar involvement, (2) antero-posterior stalk thickness <5.25 mm, (3), presence of DI, and (4) presence of a diffusely thickened PS. With these 4 parameters, they were able to accurately classify 87.3% of their patients [65]. Conversely, in a study by Sbardella et al. [66] on 36 patients (26 adults), the presence of DI was more in favor of neoplastic lesions (80 vs. 35%). Higher textural heterogeneity was also found in neoplastic lesions compared with inflammatory lesions on pre- and postgadolinium T1W images.

In case of negative intracranial and whole-body evaluation, if the lesion is limited to the PS, it could be proposed, before resorting to a PS biopsy, to watch the lesion by repeating MRI and reevaluating clinical, hormonal and imaging status, usually after 3–12 months.

A study of 85 children and young adults with DI and PS thickening evaluated optimal biochemical and imaging follow-up. The great majority of patients with PS thickening developed anterior pituitary defects within the first 24 months after the onset of DI. They conclude that pituitary function should be assessed every 6 months during the first 2–3 years and yearly afterwards. Neuroimaging assessment should be performed every 6 months for the first 2 years, at the third year, and then withdrawn afterwards [67]. A second MRI in suspected cases of isolated stalk enlargement can certainly be proposed even earlier, 3–6 months after the initial evaluation.

In the case of radiological progression or suspicion of tumor, diagnostic biopsy or resection is indicated. The approach is often transcranial, but less invasive routes, such as endoscopic assisted microsurgery via the supraorbital keyhole, have been suggested [68]. Despite precise diagnostic and thorough watch and revaluation strategies, approximately one-third of cases will still remain undiagnosed, even in specialized centers of excellence (Table 1).

Conclusion

PS enlargement may be due to various etiologies, and the main concern is to differentiate neoplastic malignant causes and benign, inflammatory causes; biopsy of the PS is difficult, invasive and harmful. Making the correct diagnosis is not always straightforward, and an extensive workup looking for lesions outside the hypothalamo-pituitary region, often easier to biopsy, is helpful. However, tumoral etiology, limited to the PS, should always be questioned. Repeated imaging and hormonal evaluation are often necessary, and in many cases, the underlying pathology will still remain unknown.

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S.S. and P.C. prepared the material for this review. V.H. wrote the first draft. P.C. prepared the final draft.

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