Inflammatory and granulomatous expansive lesions of the pituitary

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Inflammatory and granulomatous diseases of the pituitary are rare causes of sellar masses. Lymphocytic hypophysitis is the most relevant of these disorders, and it is characterised by autoimmune pathogenesis with focal or diffuse inflammatory infiltration and varying degrees of pituitary gland destruction. Endocrine symptoms may include partial or total hypopituitarism, with adrenocorticotropic hormone (ACTH) deficiency being the earliest and most frequent alteration.

Pituitary abscess is a rare but potentially life-threatening disease and, in 30–50% of patients, anterior pituitary hormone deficiencies or central diabetes insipidus (DI) at onset may be observed: the earliest manifestation being growth hormone deficiency (GHD), followed by follicle-stimulating hormone (FSH)/luteinising hormone (LH), thyroid-stimulating hormone (TSH) and ACTH deficiencies. Fungal infections of the pituitary are also very rare and include aspergillosis and coccidioidomycosis. Concerning pituitary involvement in systemic diseases, in sarcoidosis endocrine complications are rare, but the hypothalamus and pituitary are the glands most commonly affected. DI is reported in approximately 25–33% of all neurosarcoidosis cases and is the most frequently observed endocrine disorder. Hyperprolactinaemia and anterior pituitary deficiencies may also occur.

Rarely, partial or global anterior pituitary dysfunction may be present also in Wegener’s granulomatosis, either at onset or in the course of the disease, resulting in deficiency of one or more of the pituitary axes. Other forms of granulomatous pituitary lesions...
The hypotalamic–pituitary system is involved mainly in children with Langerhans’ cells histiocytosis who develop DI, which is the most common endocrine manifestation. Anterior pituitary dysfunction is found more rarely and is almost invariably associated with DI. Pituitary involvement may also be observed in another form of systemic histiocytosis, that is, Erdheim–Chester disease. Tuberculosis is a rare cause of hypophysitis, which may present with features of anterior pituitary dysfunction, such as hypopituitarism with hyperprolactinaemia.

In conclusion, in patients with a sellar mass and unusual clinical presentation (DI, neurological symptoms), aggressiveness and onset and in the presence of systemic diseases, inflammatory and granulomatous pituitary lesions should be carefully considered in differential diagnosis.

In the differential diagnosis of sellar lesions, inflammatory and granulomatous diseases of the pituitary should be considered (Tables 1 and 2).

Inflammatory sellar lesions do not present with hypersecretory symptoms (with the exception of hyperprolactinaemia secondary to stalk compression) but rather with neurological or endocrine symptoms (hypopituitarism) as a result of the mass-effect mechanism.

Neurological symptoms include headache, visual disturbance, cranial neuropathy, hydrocephalus and mental changes. Hypopituitarism most often is characterised by growth hormone (GH) deficiency and gonadal dysfunction, followed by secondary hypothyroidism and adrenal insufficiency. Diabetes insipidus (DI) is general suggestive of non-adenomatous sellar lesions.

### Inflammatory lesions

**Lymphocytic hypophysitis**

Lymphocytic hypophysitis (LYH) is a disorder characterised by focal or diffuse inflammatory infiltration and varying degrees of pituitary gland destruction.

LYH, often referred to as autoimmune hypophysitis, is seen more frequently in women and may be sub-classified into three types: lymphocytic adenohypophysitis (LAH), lymphocytic infundibuloneurohypophysitis (LINH) and lymphocytic panhypophysitis (LPH).

Although there is still some debate, an autoimmune pathogenesis is suggested by several histopathological, laboratory and clinical findings. The first histopathological observations derived from autoptical or post-surgical pituitary examinations, as well as in more recent reports, specimens have

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<td><strong>Etiological classification of inflammatory pituitary lesions.</strong></td>
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<td>A) Autoimmune</td>
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<td>- Lymphocytic hypophysitis</td>
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<td>- Lymphocytic adenohypophysitis (LAH)</td>
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<td>- Lymphocytic infundibuloneurohypophysitis (LINH)</td>
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<td>- Lymphocytic panhypophysitis (LPH)</td>
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been obtained by trans-sphenoidal pituitary biopsy, which is thought to be the gold diagnostic standard for LYH.5

An autoimmune aetiology of LYH is also supported by the frequent association with other autoimmune conditions: the most common is with autoimmune thyroid disease reported in 15–25% of LYH cases.6,7 Of these, about 75% are chronic autoimmune thyroiditis.5 The role of anti-pituitary antibodies (APAs) in LYH has yet to be clarified, but their detection has refined the diagnostic criteria.4,8–11 PRL cell autoantibodies were the first to be detected by immunofluorescence, antibodies to other pituitary-hormone-producing cells (often, however, with low sensitivity and specificity) were subsequently detected; in particular, antibodies to ACTH-secreting cells were detected in some patients with isolated ACTH deficiency.12 Auto-antibodies to GH-secreting cells were first detected by Bottazzo et al.13 in a patient with Turner’s syndrome, partial GH deficiency (GHD) and a familial history of autoimmune polyendocrinopathy. These antibodies have also been detected in a few prepuberal subjects with idiopathic short stature or idiopathic GHD,8 and De Bellis et al.14 suggested that high-titre APAs are a good diagnostic tool to reveal the occurrence of GHD15 in adults with autoimmune endocrine diseases.

Auto-antibodies against pituitary hormones have been detected in several other clinical conditions such as Graves’ disease16, premature ovarian failure17 and anorexia or bulimia nervosa.18 Furthermore, auto-antibodies against the ubiquitous glycolytic enzyme alpha-enolase and neuron-specific enolase (NSE) have been found in the serum of patients with LYH.19–21 Currently, clinical relevance of the measurement of pituitary antibodies is still limited, and their assays are not available for routine diagnostic purposes but are mainly used as research tools.

Histopathology remains the gold standard for diagnosis of LYH, in fact, a diffuse polyclonal lymphocytic infiltration with predominance of T cells, particularly CD4 cells, is characteristic.3,22 Of the reported cases of LAH, 80–90% are women in pre-menopausal period5,7,23; the mean age at diagnosis is 34.5 years for females and 44.7 years for males.23 LINH exhibits a balanced sex distribution, with a mean age at diagnosis as 47.3 ± 17.4 years5 even if it can occur also in the elderly24 and in children.25 LYH is rare in the Japanese population, but not in Caucasian, with a Caucasian to Japanese ratio of about 3:1.7

LYH seems to be strongly correlated with pregnancy22,26; in fact, it frequently affects women in the last 6 months of pregnancy and in the first 6 months after delivery.5,7,27 However, in recent years, reports of LYH cases occurring without association with pregnancy have increased; this also suggests a higher prevalence of the disease than previously thought.26

Clinical symptoms of LYH include: headache and impaired vision (50–70% of cases), nausea or vomiting and fatigue (25%), weakness and anorexia (15%), visual disturbances (40%), decrease in visual acuity (16%) and diplopia (< 10%).5,7,26 Endocrine symptoms may include partial or total hypopituitarism (66–97% of cases).4 Interestingly, impaired secretion of ACTH seems to be the earliest and most frequent alteration, and it is present in about 65% of cases.7 Isolated ACTH deficiency28 may be observed also in combination with other autoimmune diseases such as type 1 diabetes.29 In rare cases, acute

| Table 2 |
| Etiological classification of granulomatous pituitary lesions. |

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<thead>
<tr>
<th>A) Idiopathic</th>
<th>B) Systemic granulomatous diseases</th>
<th>C) Systemic histiocytosis</th>
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<tr>
<td>- Giant cell granulomatous hypophysitis¹</td>
<td>- Sarcoidosis</td>
<td>- Langerhans’ cell histiocytosis</td>
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<td></td>
<td>- Wegener’s granulomatosis</td>
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<td></td>
<td>- Takayasu’s disease²</td>
<td>- Erdheim-Chester disease</td>
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<td>- Cogan’s syndrome²</td>
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<td>- Chron’s disease²</td>
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¹ Diagnosis when systemic diseases are excluded
² Single case reports available
secondary hypoadrenalism may be the presenting feature of the disease, with high mortality of affected patients. LYH can also cause TSH and/or gonadotropin deficiencies, which are usually misdiagnosed when LYH affects women in pregnancy or in the post-partum period, whereas data on the effects on the GH/IGF-1 axis are inconclusive. In fact, reversible GHD may be observed in patients with isolated ACTH deficiency during glucocorticoid replacement. Hypopituitarism involving almost all hormones usually occurs when the inflammatory process induces pituitary tissue destruction. Hyperprolactinaemia affects approximately one-third of patients (20–38%). Probably, a multifactorial aetiology related to the diffuse inflammatory process can be evoked for hyperprolactinaemia, namely loss of the inhibitory effect of dopamine and alteration of dopamine receptors, lactotrophe hyperplasia or escape of prolactin into the circulation secondary to the massive cellular destruction. Some patients with LYH can present with hypoprolactinaemia. DI is present in about 14–20% of the cases; when the neurohypophysis is involved, the presence of DI is more frequent. Based on these data, it can be suggested that when LYH is suspected, basal and dynamic hormonal pituitary secretions have to be studied to disclose subclinical or overt alterations.

The natural history of LYH is thought to progress from inflammation to fibrosis and subsequent atrophy (occasionally apoplexy) of pituitary gland, which can later present as an empty sella in imaging studies, although spontaneous remission has been reported in several cases. Moreover, in LINH, the inflammatory process can be self-limited in about 2 years time, although complete or partial central DI may be permanent.

Magnetic resonance imaging (MRI) often shows symmetric enlargement of the pituitary gland with homogeneous contrast enhancement. Specific MRI findings may include in LAH an intrasellar mass with marked contrast enhancement; diffuse, ill-defined, symmetrical pituitary enlargement; suprasellar ‘tongue-like’ extension. Delayed complete enhancement time is observed at dynamic MRI. In LINH, together with diffuse thickening of the pituitary stalk, with or without enhancement after gadolinium, loss of the normal posterior ‘bright spot’ on T1-weighted images is observed.

The differential diagnosis of LYH includes pituitary adenomas, Sheehan’s syndrome, inflammatory pseudotumours, granulomatous and xantomatous hypophysitis and infectious hypophysitis (abscess or tuberculosis). Glucocorticoids have been reported to be effective in LAH and LIHN. In LYH, 62.5% of patients who received pharmacological doses of GC showed reduction of pituitary mass, whereas 44.4% of patients who received only physiological doses showed reduction of pituitary mass. The effect has been reported to be more favourable in patients with short standing disease (less than 6 months) and also pulse therapy with high-dose methylprednisolone has been suggested. In specific cases with poor response to corticosteroids other immunosuppressive agents have been used, such as azathioprine, methotrexate and cyclosporine A.

If neurological symptoms do not improve with medical treatment, trans-sphenoidal surgery for diagnostic confirmation and decompression is advised. A peroperatory frozen section cytology has been suggested to confirm the diagnosis and in order to avoid extensive unnecessary surgery. Immediate surgery may be necessary when there are signs of optic nerve compression or increased intracranial pressure. Stereotactic radiotherapy should be reserved for cases with severe mass effect symptoms, who show poor response or who are poor candidates for high-dose corticosteroid and/or surgical treatment.

Infectious diseases

Pituitary abscess

Pituitary abscess is a rare but potentially life-threatening disease. Primary abscesses represent two-thirds of the cases and occur in a previously normal pituitary, whereas secondary abscesses arise in an already compromised pituitary gland. Only a few hundred cases have been reported in the literature in the last century, with the majority of them published as case reports.

Primary pituitary abscess may develop in an otherwise normal pituitary gland, either due to haematogenous seeding or by direct extension of adjacent infection, either in the sphenoid sinus, or
more rarely as a complication of thrombosis of the cavernous sinus. Secondary pituitary abscesses occur in glands that harbour a pre-existing lesion; other risk factors are immunocompromised conditions and previous pituitary surgery or irradiation.

In the case series of Vates et al., the most common presenting symptom was long-standing (>2 months) headache; moreover, visual disturbances (50%), signs of meningism (25%), fever or leucocytosis (33%) have been reported. According to the literature, about 30–50% of patients have anterior pituitary hormone deficiencies or central DI at onset: the earliest manifestation appears to be GHD, followed by follicle-stimulating hormone (FSH)/luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) deficiencies. Dalan et al. found that anterior panhypopituitarism was present in 60% of patients, central DI in 28% and hyperprolactinaemia in 15%.

Pituitary abscess most often presents with a chronic and indolent course, with paucity of infective manifestations, but frequently mimics a pituitary tumour instead. However, mortality can reach 30–50% of cases when the clinical course of the pituitary abscess is complicated by meningitis. Even in the absence of any overt sign of infection, pituitary abscess should be considered in differential diagnosis with pituitary adenoma, carcinoma, arachnoid cyst, colloid cyst, Rathke cleft cyst, craniopharyngioma and metastasis. In fact, on MRI, pituitary abscess may present as a round sellar cystic lesion, hypo- or isointense on T1 pre-contrast imaging and hyper- or isointense on T2 imaging with peripheral gadolinium enhancement.

Diagnosis usually is made during surgical exploration when pus is found in a cystic lesion. Culture of the abscess material identifies pathogens in only half of the cases; as a matter of fact, the most common pathogens are Gram-positive bacteria. Treatment consists of surgical drainage and antibiotic administration for 2–6 weeks. Trans-sphenoidal approach avoids cerebral contamination and for this reason is the preferred approach.

The recovery of the endocrinological abnormalities after treatment is variable, with complete resolution in a few cases and persistent abnormalities (anterior and posterior panhypopituitarism) in most of the cases.

**Fungal infections**

Fungal infections of the pituitary are rare. Aspergillosis belongs to the group of mycotic diseases of paranasal sinuses; it frequently extends into the orbital region, where it may involve the optic nerve. Invasion of the skull base regions has also been reported. The invasive forms are usually observed in immune compromised patients. In fact, granulocytopenia, especially neutropenia, is one of the predisposing factors for acute invasive and fulminant aspergillosis. Other risk factors are immune deficiency syndromes (HIV) and iatrogenically induced immune suppressive status after organ and bone marrow transplantation.

Aspergillosis of the sphenoid sinus extending into the sellar region and simulating a pituitary tumour is extremely rare. Only sporadic cases, although not only in immunodeficient patients, have been reported in the English literature. The symptoms of invasive aspergillosis are dependent on the type and extent of destruction of the anatomical structures. Ocular muscle paraesthesia with diplopia, to the extent of ophthalmoplegia and ptosis may be observed (cavernous sinus syndrome). Suprasellar invasion may cause visual acuity and field loss, even to the extent of blindness. Non-specific headache or pyrexia was reported. Imaging studies include Rx of the skull, computed tomography (CT) and MRI of the paranasal sinuses and skull base.

The final diagnosis of aspergillosis of the frontal skull base is only made as a result of surgical exploration of the invaded areas. Surgical treatment should aim more at radically removing the mycotic infected lesion, rather than draining it. Moreover, local lavage with fluconazol through an implanted drain, as well as second-look surgery, has been reported. If a macroscopically total resection is not possible, an antymycotic therapy with Amphotericin B, Rifampicin, lipid-capsuled Amphotericin B, Itraconazole, Caspofungin or Voriconazole should be administrated. The value of postoperative antymycotic therapy is controversial.

Another rare fungal infection that can simulate a pituitary adenoma is coccidioidomycosis: the onset may be acute with unilateral ophthalmoplegia. Radiological studies may again indicate a mass
lesion involving the pituitary gland and cavernous sinus. The trans-sphenoidal approach and histological work-up reveal the presence of Coccidioides granuloma. This pathological entity should be considered when evaluating patients with a pituitary mass and ophthalmoplegia.58

**Tuberculosis**

Tuberculosis (TBC) is a cause of secondary granulomatous infectious hypophysitis in the developing world. Histopathologically, tubercolous hypophysitis is classically characterised by a central area of necrosis surrounded by epithelioid macrophages, lymphocytes, plasma cells and Langheran’s giant cells.59 TBC is a relatively common disease in developing countries but tubercular infections in the central nervous system (CNS) are not frequent, and therefore, pituitary TBC is rare;59 in fact, intracranial TBC accounted for 30–50% of intracranial lesions before the era of chemotherapy; conversely, nowadays, it accounts for 0.15–4% of all cases.1

Tubercular hypophysitis, as well as lymphocytic hypophisitis, often presents with features of anterior pituitary dysfunction, such as hypopituitarism with hyperprolactinaemia that causes galactorrhoea and amenorrhoea in females and decreased libido in males.30 DI with polyuria and polydipsia is often observed.60 Headache is the most common and usually one of the early symptoms noted in affected individuals associated with visual disturbances.1,59

Other signs of active TBC are generally but not invariably present.1 At MRI, pituitary tuberculoma presents with features suggestive of a sellar mass; thickening and nodularity of the pituitary stalk are considered to be a sign of pituitary tuberculoma, but this finding is not specific since it can be also seen in other inflammatory conditions such as sarcoidosis and idiopathic hypophysitis.59–61 Surgery is not usually indicated in tubercular hypophysitis, except for obtaining biopsies to confirm diagnosis. Trans-sphenoidal route is the safest route to avoid cerebrospinal fluid contamination.62

Anti-tubercular treatment is mandatory, and hormone replacement therapy may be necessary in the few cases that present with symptoms of hypopituitarism.1,59 Rifampicin, which is widely used as anti-tubercular treatment, induces cytochrome CYP3A4, which metabolises glucocorticoids in the liver.63 Therefore, use of rifampicin may be associated in patients with tubercular hypophisitis with the risk of decompensating corticotropin deficiency and potential addisonian crisis also in patients under glucocorticoid replacement.63,64

**Granulomatous lesions**

**Sarcoidosis**

Sarcoidosis is a chronic multi-systemic disease of unknown aetiology, characterised by the formation of immune granulomas in the organs involved.65 This disorder can affect individuals of both genders and almost all ages, but mainly young and middle-aged adults. There is evidence that various antigens may promote sarcoidosis in generally genetically and immunologically susceptible individuals, and this may account for the diversity of disease expression; however, non-causative agents for such inflammation such as infectious agents, metal dusts and organic antigens have been identified. The clinical impact of the disease is dependent on the site of granulomatous inflammation and its severity through the body.65 The organs involved more commonly are the lungs, skin and lymph nodes. Multi-systemic localisations or complications, such as severe pulmonary fibrosis, or pulmonary hypertension, or cardiac and neurological involvement can be life-threatening.65,66

Endocrine complications are rare in sarcoidosis, but the hypothalamus and pituitary are the glands most commonly affected.67 DI is reported in approximately 25–33% of all neurosarcoidosis cases68 and is the most frequently observed endocrine disorder with polyuria and polydipsia being reported by 17–90% of patients according to different series.67–69 Hyperprolactinaemia also occurs commonly as the result of loss of dopaminergic inhibition30 being reported by 3–32% of the patients.67,69 Anterior pituitary deficiencies, mainly hypogonadism, may also be observed.70 In a recent review, Bihan et al. evaluated pituitary dysfunction and imaging of the hypothalamic–pituitary area in a personal series of
patients and in the literature both at diagnosis of sarcoidosis and after treatment. These authors found among hormonal deficiencies associated with hypothalamic–pituitary sarcoidosis hypogonadism to be the most frequent, followed by DI. Findings included the absence of normal T1-weighted hyperintense signal. The pathological lesions were reported to be isointense on T1-weighted images and enhanced by gadolinium. MRI abnormalities improved or disappeared in seven cases under corticosteroid treatment, but in most, even if not all, cases endocrine defects were irreversible despite regression of the granulomatous process, probably for a permanent cellular damage. The same authors concluded that, in patients with sarcoidosis, pituitary hormonal evaluation and MRI of the sella should be performed once a year, and after any changes of therapy.

**Wegener’s granulomatosis**

Wegener’s granulomatosis (WG) is a systemic disorder characterised by necrotising granulomatous small-vessel vasculitis. The aetiology of this disorder is unknown, but it is closely associated with anti-neutrophil cytoplasmic antibodies (ANCAs) and specifically proteinase 3 (PR3) ANCA. Although WG in general occurs in equal proportion in men and women, there are more female patients (74%) reported with pituitary involvement.

WG typically affects a combination of ear, nose and throat, lung and kidneys, and may also affect joints, skin, eyes and virtually any tissue or organ. Pituitary involvement in WG is rare; in fact, it has been documented in less than 1% of affected subjects and predominantly concerns the posterior pituitary leading to central DI. Rarely, partial or global anterior pituitary dysfunction may be present, either at onset or in the course of the disease, resulting in deficiency of one or more of pituitary axes. The suggested causes of this complication include vasculitis of pituitary vessels, granulomatous lesions in situ or extension to the nervous system of adjacent nasal or paranasal granuloma. According to Yong et al., clinical features related to pituitary involvement were present at onset in eight of the 23 observed cases and preceded other organ involvement in three patients. The extent of pituitary involvement was variable: about half of the patients had only central DI (with or without hyperprolactinaemia, which was likely due to stalk disruption) whereas one-third of them had both anterior and posterior pituitary involvement, including panhypopituitarism and only a minority of the patients had only anterior pituitary functional abnormalities.

MRI usually shows an enlarged pituitary gland with homogeneous enhancement and thickening of infundibulum, especially in the superior portion. The majority of patients respond to medical management, such as corticosteroids and immunosuppressors (cyclophosphamide) associated with hormonal replacement. Several cases show complete resolution of DI under control of WS; other patients have demonstrated persistent DI in spite of improvement of peripheral manifestations of the disease and even reduction of hypothalamic granulomatous lesions.

**Other forms of pituitary granulomatosis**

Pituitary granulomatous involvement has been described in isolated case reports to be associated with other systemic diseases such as Crohn’s disease (with hypopituitarism, progressive bitemporal haemianopia and intrasellar mass; pathogenetic association is still uncertain), Takayasu’s disease (pituitary mass, hypopituitarism and DI in a patient with multiple arterial occlusive disease) and Cogan’s syndrome (pituitary enlargement, DI and secondary hypothyroidism in a patient with autoimmune vasculitis, ophthalmic and vestibulo-auditory lesions). When a pituitary mass in a patient with anterior hypopituitarism and DI is found to be at biopsy a giant cell granuloma and all systemic granulomatous diseases are excluded, a diagnosis of idiopathic giant cell granulomatous hypophysitis may be made.

**Langerhans’ cell histiocytosis**

Langerhans’ cells histiocytosis (LCH) is a rare disease characterised by aberrant proliferation of specific dendritic cells, called Langerhans’ cells, belonging to the monocyte–macrophage system. These
cells can infiltrate and destroy many sites, such as bone, lung, skin, hypothalamic–pituitary unit, and, less frequently, liver, spleen and lymph nodes. The course of the disease is fairly unpredictable, since it can resolve spontaneously or progress to a disseminated form, compromising vital functions with occasionally fatal consequences. 79,80

LCH is more often encountered in children, with a peak age range of 1–3 years and an incidence of 3–5 cases per million per year, with a male-to-female ratio of 2:1. 80 LCH in adults is even rarer, with an estimated prevalence of 1–2 cases per million; although LCH in the adults can develop at any age, the mean age at the diagnosis is 33 years. 81 Early and accurate diagnosis is important because multi-system LCH is associated with a 20% mortality rate, and 50% of those who survive develop at least one permanent consequence. 82

The hypothalamic–pituitary system is involved in 5–50% of children with LCH and 17–25% of them develop DI, which is the most common endocrine manifestation. 83,84 DI usually develops within a year after the diagnosis of LCH, but it can occur at any time during the course of the disease. In fact, DI can also be the presenting feature of LCH 85,86; about half of the patients presenting with DI will develop other LCH manifestations within a year. 86 The pathogenesis of DI, as well as of other pituitary dysfunctions, has been attributed to either infiltration and/or scarring of the hypothalamic–pituitary system or to an autoimmune process involving reacting antibodies against vasopressin. 87 Established DI is generally permanent and, when not remitting after any available treatment, needs substitutive treatment. 85–87

Anterior pituitary dysfunction is found in up to 20% of patients with LCH and is almost invariably associated with DI; only a few cases of partial anterior pituitary hormone deficiency without DI have been described so far. 83–88 Once established, anterior pituitary deficiencies seem to be permanent and are not affected by any LCH-directed treatments 83,84; therefore, appropriate hormone replacement therapy is mandatory. 89 GHD15,90 is the most frequent anterior pituitary hormone deficiency, affecting up to 42% of patients with LCH and DI 91,92, and it is usually the first anterior pituitary hormone deficiency to develop in addition to DI, with a median latency of 1 year from the diagnosis of DI. 83,84 In a recent study of 589 patients with childhood-onset LCH, GHD developed in 61 and followed the initial diagnosis by a mean of 5 years. 93 In adult series, GHD was found to be present in 53–67% of patients and was always associated with DI. 83,84 Gonadotropin deficiency is the second most common anterior pituitary hormone deficiency in adults with LCH. 83,84 It develops with a median latency of 7 years from the diagnosis of DI and 9 years after the initial diagnosis of LCH. Only few data are available on the gonadal function in adults, revealing a 53–58% prevalence of gonadotropin deficiency always associated with DI. Similar to other LCH-induced anterior pituitary hormone deficiencies, gonadotropin deficiency is considered to be permanent 83,84,95, although occasionally spontaneous recovery has been reported. 96

ACTH deficiency is described in 1–2% of LCH patients, mostly in the context of generalised pituitary involvement and panhypopituitarism 83,84; however, ACTH deficiency has also been described in LCH patients without panhypopituitarism. 93–95 This relative low prevalence of ACTH deficiency might be due to the lack of adequate endocrine evaluation, and it is likely that cases of mild and/or subclinical ACTH deficiency could have been missed. 95 Because ACTH deficiency is a potentially life-threatening situation, it has been suggested to evaluate the HPA axis in all LCH patients with evidence of pituitary involvement. 84 TSH deficiency can also be a major component of anterior pituitary dysfunction in patients with LCH. According to some authors, it is always associated with panhypopituitarism 83, whereas other authors report TSH deficiency to be the third most frequent pituitary hormone deficiency (3.9% of all patients), following DI and GHD, in large series of childhood-onset LCH. 93 Moderately elevated PRL levels have recently been reported in several adult patients. 83 This may be either attributed to infundibular infiltration or concomitant gonadotropin deficiency. 97 Because several studies have shown that endocrine deficiencies can evolve during the course of the disease, it is advised that patients with isolated or partial pituitary hormone deficiency should be monitored at regular intervals. 83,84,93,94

On MRI, pituitary stalk thickening (>3.5 mm) and absence of the normal hyperintense signal of the posterior pituitary (bright spot) are the most common findings. 83 An isolated hypothalamic lesion can be present. 98,99 Pituitary stalk biopsy is not recommended routinely in lesions smaller than 7 mm because of the risk related to this procedure. 98
Combination of vinblastine with steroids is the most frequently used initial therapy for multisystem disease in adults, and it is the current standard treatment in multisystem disease in children as well.\textsuperscript{100} Radiotherapy, at doses up to 25 Gy, has been used in patients with endocrine deficiencies and radiological evidence of hypothalamic–pituitary involvement and has been associated with partial or temporary radiological improvement only.\textsuperscript{83}

**Erdheim–Chester disease**

First described in 1930\textsuperscript{101}, Erdheim–Chester disease (ECD) appears to be rare, with less than 100 cases in the published literature.\textsuperscript{102} Even though the pathological hallmark of ECD is infiltration of a wide variety of tissues by cells of macrophage and histiocyte lineage, it appears to be distinct from LCH.\textsuperscript{101} In fact, histologically, it is an infiltrative process consisting of a preponderance of lipid-laden histiocytes or foam cells intermixed with lymphocytes and eosinophils.\textsuperscript{103,104} Erdheim–Chester disease is protean in its manifestations, with a course ranging from a focal indolent process to a full-blown, multi-organ and life-threatening condition. Moreover, involvement of any organ system can occur, although the gastrointestinal tract and the spleen appear to be relatively spared.\textsuperscript{101,102}

This disease is more frequently reported in adult subjects\textsuperscript{101,102} with respect to LCH. Some endocrine manifestations of ECD have been noted, predominantly in the orthopaedic, radiological and pathological literature, with particular emphasis placed on the occurrence of central DI.\textsuperscript{105}

However, hypopituitarism and hyperprolactinaemia have also been reported.\textsuperscript{103} At MRI, pituitary mass lesions or stalk thickening is rarely found\textsuperscript{103,106}, but the normal bright spot is frequently absent from the posterior pituitary on T1-weighted sagittal and coronal images, both at baseline and after gadolinium.\textsuperscript{103} Prolactin cell hyperplasia may be the only finding in the adenohypophysis of patients with disseminated ECD. It appears that in patients with clinically apparent anterior hypopituitarism, this is not due to the lack of storage but rather to insufficient release of adenohypophysial hormones caused by the defect in hypothalamic regulation.\textsuperscript{107} It should be noted that various treatments have been tried for ECD\textsuperscript{101–103}, including steroids, chemotherapy (vinblastine alone, or in combination with doxorubicin or cyclophosphamide), immunotherapy with interferon alpha-2a and radiation therapy. However, all these therapeutic modalities demonstrated partial efficacy in small numbers of patients, and the overall prognosis for patients with this disorder appears to be poor.

**Conclusions**

Inflammatory and granulomatous pituitary lesions are uncommon causes of pituitary enlargement and dysfunction. However, particularly the studies on lymphocytic hypophysitis induced a remarkable progress in the pathophysiological knowledge of several pituitary diseases.

Clinically, the endocrinologist should be aware that, in cases with unusual presentation (DI, neurological symptoms), aggressiveness and onset and in the presence of systemic diseases, the neuroradiological finding of a sellar mass may not always mean the presence of a pituitary adenoma, and inflammatory and granulomatous lesions should be carefully considered in differential diagnosis. Finally, the correct diagnosis of these lesions is mandatory due to the often peculiar responses of pituitary lesions to the treatment of the underlying disease.

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