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Review

Diagnosis and classification of autoimmune hypophysitis

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ABSTRACT

Autoimmmune hypophysitis (AH) is the consequence of an immune-mediated inflammation of the pituitary gland. The initial pituitary enlargement, secondary to infiltration and oedema, can evolve to remission, for spontaneous or pharmacological resolution of the inflammation, or evolve to progressive diffuse destruction with gland atrophy for fibrotic replacement, thus leading to various degrees of pituitary dysfunction. The autoimmune process against the pituitary gland is made evident by the appearance of circulating autoantibodies (APA), mainly detected by indirect immunofluorescence on cryostatic sections of human or primate pituitary. Among the target autoantigens recognized by APA are alpha-enolase, gamma-enolase, the pituitary gland specific factors (PGSF) 1 and 2 and corticotroph-specific transcription factor (TPIT). However, the low diagnostic sensitivity and specificity of APA for AH strongly limit the clinical use of this marker. AH should be considered in the differential diagnosis of non-secreting space-occupying lesions of sella turcica, to avoid misdiagnosis that may lead to an aggressive surgery approach, since endocrine dysfunction and the compressive effect may be transient.
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1. Introduction

Lymphocytic hypophysitis (LH) is an inflammatory disorder affecting anterior (lymphocytic adenohypophysitis, LAH), posterior (lymphocytic infundibuloneurohypophysitis, LINH) or both (lymphocitic panhypophysitis, LPH) pituitary lobes [1,2]. It is also commonly referred to as "autoimmune hypophysitis" (AH), because its epidemiological, histomorphological and clinical features are suggestive for an autoimmune pathogenesis [1,2]. The flogistic destruction can be self-limiting or result in permanent endocrine/neurological dysfunction, and even in potentially life-threatening complications. The first description of pituitary autoimmunity was made in 1962 by Goudie and Pinkerton [3], as an autoptycal finding of extensive lymphocytic infiltrate of anterior pituitary in a young woman affected by Hashimoto's thyroiditis, dead for circulatory shock one year after her second delivery. However, it is likely that some cases of end-stage hypophysitis among Sheehan's original series of patients from the early 1900s [4] may have included cases of lymphocytic hypophysitis. In addition, Carpenter's review of Schmidt's syndrome from 1964 [5] included at least two patients studied in 1930s with autoimmune polyendocrine syndrome and lymphoid infiltration of the hypophysis. After the first enunciation by Goudie and Pinkerton, autoimmune hypophysitis has been referred to in the literature with a variety of different names, though the most common terms remain LH/LAH, or LINH when diabetes insipidus (DI) is associated. Nevertheless, though evidence of global glandular involvement has been documented from 1991, to consider LAH and LINH as aspects of the same nosologic entity with a common pathogenesis is still challenging, because of their different structural, histological and onthogenetic characteristics.

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The gold standard for unequivocal diagnosis remains pituitary biopsy, but similarly to what occurred for other endocrine autoimmune diseases, the search for pituitary autoantibodies, with the aim of developing accurate and non-invasive diagnostic tests of the disease, is very active.

The demonstration of the existence of pituitary autoantibodies was first provided in 1965 [6] in sera from patients with Sheehan's syndrome, by using a complement consumption test. From 1970 [7], several case reports have documented the same histo-pathological features, though limited to infundibulum stem and neurohypophyseal tissue, in patients presenting with diabetes insipidus.

2. Epidemiology

The prevalence and incidence of LH are not known with precision. Discrepancies in the way diagnosis is formulated, e.g. pituitary biopsy vs. clinical picture, make it problematic to generate accurate epidemiological estimates. AH is considered a rare condition, although reported with increasing frequency in the last years. The extrapolated incidence on overall population is low, approximately 1 in 9 million/year [1], but probably underestimated. LAH is more common in women and has an established, strong association with late pregnancy and postpartum (from 30 to 70% of cases) [1,2,8,9]. Mean age is third-fourth decade. No strict female predisposition is reported for LINH and LPH, though a weak female predisposition has been reported for LPH [1].

In large series of pituitary surgery, LH accounted for approximately 0.24 to 0.88% of cases [1,10]. However, these estimates may represent only those cases that presented more acutely. In the largest series of 2500 surgical pituitary cases, collected in Germany between 1970 and 1996 [10,11], LH was identified in 6 cases (0.24%). Honegger et al. [12] found 7 cases of hypophysitis among 2362 pituitary cases (0.3%). Similarly, a review of 2000 pituitary cases from Virginia, US [13] identified 16 patients with hypophysitis, but only in 10 a definitive diagnosis of LH was made according to a pituitary biopsy. Higher frequencies were observed in a study from Nottingham (0.8%) [14] and in a study from the Johns Hopkins Hospital (0.88%) [1].

3. Pathogenesis and histopathological findings

LH is thought to have in many cases an autoimmune origin [1–3]. Association with other autoimmune diseases has been reported in 25–50% of cases [1,15–18]. The most common association is with Hashimoto's thyroiditis (with an estimated frequency of 7–8%) [3,15,19], but LH has been diagnosed in patients with Graves' disease [18,20], Addison's disease [21], type 1 diabetes mellitus [16,18], atrophic gastritis [18,22], systemic lupus erythematosus [23,24], Sjögren's syndrome [25], primary biliary cirrhosis [26], autoimmune hepatitis [27] or autoimmune polyendocrine syndrome type I/autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) [28]. The autoimmune process likely targets specific pituitary cell sub-types, with early selective loss of ACTH, FSH/LH or TSH secreting cells and subsequent triggering of an unselective destruction of the gland. Concerning the association with pregnancy, both changes in immunologic system modulation and in pituitary volume or its blood supply may play a major role [1].

At autopsy, the pituitary gland of patients with LH showed significant atrophy [17], associated with secondary atrophy of adrenal glands. At neurosurgery, pituitary tissue is more often fibrous, adherent to surrounding structures and dura mater. At histopathology, LH is characterized by extensive lympho-plasmacytic infiltration of anterior pituitary. Inflammatory cells are T and B cells with a proportion of plasma cells and occasional eosinophils, macrophages, histiocytes [10,11,29–31] and mast cells [32]. T-cells predominate over B-cell infiltrates in areas characterized by lymphoid follicles. The $CD4^+/CD8^+$ cell ratio has been described to be 2:1, or greater, in most cases [11,32–36]. Preferential expression of activated $CD8^+$ T cells was observed in pregnant women with a short duration of disease symptoms [30].

4. Clinical manifestations

Clinical findings may vary according to the rapidity of progression of the disease process. LH is predominant in females, with a female:male ratio of 6:1 [1], and disease presents at a younger age in females than in males [2]. In addition, there is a strong association with pregnancy. LH may present as an acute, subacute or chronic condition. Acute manifestation of LH is similar to that of a non-secretory pituitary tumour with adrenocorticotrophin (ACTH) deficiency and secondary adrenal insufficiency. The rapidity and severity of disease progression explain cases of sudden death reported in the literature [37,38]. The reasons why ACTH deficiency is more common and precocious in LH than in pituitary adenoma are unclear. Acute LH is also often characterized by TSH deficiency and rarely may also present with symptoms of pituitary apoplexy [39].

Subacute LH is typically observed in young women during pregnancy or post-partum [18,19]. In this scenario, symptoms and signs are those of a pituitary mass that resolves at follow-up. The MRI typically demonstrates an increased hypophysis with uniform enhancement after magnetic contrast administration with possible extension to the hypothalamus. Hormonal changes are much less dramatic than in the acute manifestation of the disease. Prolactin may be increased, normal or reduced in approximately equal proportions [1,40]. In the case of hyperprolactinemia, differential diagnosis with a prolactinoma may be challenging. In contrast with what was observed in other pathological conditions of the pituitary gland, such as brain trauma or irradiation [41,42], in which GH deficiency is one of the first deficits, secretion of GH is more frequently preserved in subacute LH.

In acute or subacute LH, extension of the inflammatory process to the surrounding structures may occur. Involvement of the cavernous sinus is responsible for headache and diplopia, associated with third, fourth or six cranial nerve palsies. Dural involvement is often observed at MRI scans and may require differential diagnosis with hyperthrophic cranial pachymeningitis [25]. Significantly higher lymphomonocytic pleocytosis was observed at an analysis of cerebrospinal fluid in patients with suspected LH as compared to patients with documented pituitary adenoma [43], which suggests a possible association with aseptic meningitis.

Diagnosis of chronic LH is more problematic. Rarely pituitary biopsy is proposed in this scenario. The availability of an accurate autoantibody assay would be instrumental for the correct diagnosis of many chronic cases. In chronic LH, postinflammatory fibrosis may lead to pituitary gland atrophy and empty sella at MRI scan. A complicating factor is heterogeneity of empty sella syndrome. Nevertheless, isolated ACTH or TSH deficiency has been documented in patients with empty sella syndrome and autoimmune endocrinopathies. In contrast, pituitary tumours tend to cause more often isolated GH or isolated gonadotroph dysfunction. Taken together these clinical findings indirectly suggest that at least a proportion of cases of empty sella and of isolated ACTH or TSH deficiency may have an autoimmune origin.

In summary, clinical findings of LH can be divided into three groups, as reported in Table 1. Their relative frequency varies depending on whether anterior, posterior or both pituitary lobes are involved. Most patients present with symptoms related to compressive and inflammatory effects of enlarged pituitary on sellar and parasellar structures, as headache, present in over 50% of cases at diagnosis [8,9]. Among the symptoms of hypopituitarism, those ascribable to hypogonadism and hyperprolactinemia are reported with various frequencies [1,8]. With the exception of lactating women, hyperprolactinemia does not occur commonly and may be secondary to stalk compression, impaired dopamine effect for inflammation, immunological destruction of lactotrophs with PRL release, or supposed PRL-secretion stimulating autoantibodies [33]. As discussed above, symptoms of hypocorticolism are frequently

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