Endocrine (2012) 42:74–79
DOI 10.1007/s12020-012-9654-7

MINI REVIEW

Pituitary autoimmune disease: nuances in clinical presentation

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Received: 27 December 2011 / Accepted: 6 March 2012 / Published online: 17 March 2012

Abstract Pituitary autoimmune disease is considered an autoimmune organ-specific disorder, characterized by a pituitary infiltration of lymphocytes, macrophages, and plasma cells that could lead to loss of pituitary function. Hypophysitis may be secondary to systemic diseases or infections. Primary pituitary hypophysitis is classified into lymphocytic, granulomatous, xanthomatous, mixed forms (lymphogranulomatous, xanthogranulomatous), necrotizing and IgG4 plasmacytic, according to the histological findings. Concerning lymphocytic hypophysitis (LH), it is characterized by lymphocytic infiltration and can be subclassified according to the affected area on: lymphocytic adenohypophysitis, lymphocytic infundibulo-neurohypophysitis and lymphocytic panhypophysitis. LH had always been considered a rare disease. Nevertheless, with improved imaging techniques, especially magnetic resonance imaging (MRI), LH diagnosis has been increased. This disease usually affects young women during pregnancy or postpartum period with headache, visual impairment, ACTH deficiency and a homogenous sellar mass with thickening of pituitary stalk in MRI. Definitive diagnosis depends on histopathological evaluation; nevertheless, a presumptive diagnosis could be done in a typical case. As no specific autoantigen was identified in LH, there is no antipituitary antibody (APA) method available for helping diagnosis. However, APA used in some centers for research could support an autoimmune origin for some hypopituitarism previously named as idiopathic, confirming nuances in clinical presentation of pituitary autoimmune disease. Therapeutic approach should be based on the grade of suspicious and clinical manifestations of LH.

Keywords Hypophysitis · Lymphocytic hypophysitis · Pituitary disease · Pituitary autoimmune disease · Hypopituitarism · Central diabetes insipidus

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Pituitary autoimmune disease is considered an autoimmune organ-specific disorder, characterized by a pituitary infiltration of lymphocytes, macrophages, and plasma cells that could lead to loss of pituitary function. Hypophysitis may be secondary to systemic diseases such as Takayasu's disease, Crohn's disease, histiocytosis, sarcoidosis, inflammatory pseudotumor, or secondary to bacterial, viral or fungal infections [1]. Interestingly enough, even local lesions such as germinoma, pituitary adenoma, craniopharyngioma, and ruptured Rathke cleft cyst may lead to hypophysitis [2]. Primary pituitary hypophysitis is classified into lymphocytic, granulomatous, xanthomatous, mixed forms (lymphogranulomatous, xanthogranulomatous), necrotizing, and IgG4 plasmacytic, according to the histological findings. In xanthomatous hypophysitis, there is an infiltrate of fat enriched histiocytes and rare lymphocytes, whereas granulomatous subtype is characterized by necrotizing granulomas with histiocytes and plasma cells in the periphery. IgG4 plasmacytic hypophysitis was first described with pathology characterization in 2007 by a mononuclear infiltration, rich in lymphocytes and plasma cells, usually with more than 10 IgG4-positive cells per high-power filed [3]. It can be associated with other organ

involvement, specially salivary glands, pancreas and retroperitoneal fibrosis. To date, twelve cases of hypophysitis related to IgG4 were described [4]. Concerning lymphocytic hypophysitis (LH), it is characterized by lymphocytic infiltration and can be subclassified according to the affected area on: lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH) and lymphocytic panhypophysitis (LPH).

LH had always been considered a rare disease. Nevertheless, with improved imaging techniques, especially magnetic resonance imaging (MRI), LH diagnosis has been increased, reaching 379 cases in 2005 [2]. In autopsy studies, lymphocytic infiltration can be found in the middle of the pituitary gland in up to 47 % of individuals. Due to the high frequency, this finding may be considered an embryonic remnant. In the other hand, the same finding in the anterior pituitary is much less common (<3 %) and thus considered pathological.

The incidence of LH is one case in 9 million persons-year, and currently, LAH is found in <1 % of pituitary surgical cases. It prevails in females (6 women: one man) and is more commonly in the fourth and fifth decades of life. The average age at diagnosis is 34.5 years for females and 44.7 for males. LAH is strongly associated with pregnancy, 57 % of cases occurring during pregnancy or postpartum period. This could be related to an increase pituitary antigens presentation to the immune system, probably due to lactotrophs' hyperplasia and increase in pituitary blood flow [2].

Clinical presentation is variable and includes symptoms related to mass compression of sellar neighborhood regions (optical chiasma, cavernous sinus), hypopituitarism, and hyperprolactinemia. In addition to these symptoms, diabetes insipidus occurs in LPH being the only clinical finding in LINH. Main symptom in LAH is headache, which usually precedes cranial nerves palsies or visual impairment. About a third of patients have hyperprolactinemia of unknown cause. The presence of anti-lactotrophs antibodies, loss of dopaminergic inhibition on lactotrophs, lactotrophs hyperplasia or escape of prolactin in the blood circulation after lactotrophs destruction are suggested as possible causes for hyperprolactinemia, frequently coexisting with hypopituitarism.

Lymphocytic hypophysitis is considered an autoimmune disease by filling three of the four criteria of Rose and Bona [5]: is reproducible in animal models, exhibits hystopathological changes as lymphocytic infiltration of T and B cells, and symptoms could be solved after immunosuppressive treatment. Nevertheless, the capability of serum from patients and animals with LH in transmitting the disease is debatable. The role of antipituitary antibodies (APA) is not well known, but it is suggested to be pathogenic.

LH may be associated to other autoimmune diseases in 20 % of cases [2] as:

(a) Endocrine diseases: Hashimoto's thyroiditis, diabetes mellitus type 1, hypoparathyroidism, Graves' disease, Addison's disease and autoimmune polyendocrinopathies;
(b) Organ-specific autoimmune: vitiligo, pernicious anemia, alopecia, myasthenia gravis, primary biliary cirrhosis, chronic atrophic gastritis;
(c) Non-organ-specific autoimmune diseases: lupus erythematosus (SLE).

Definitive diagnosis of LH depends on the microscopic examination of the pituitary tissue; nevertheless, a presumptive diagnosis can be based on the following characteristics [6]:

- Clinical: symptoms occurring during pregnancy or postpartum period; hypopituitarism disproportionate to the grade of pituitary lesion;
- Laboratory: preferential impairment of corticotroph axis; presence of antipituitary autoantibodies;
- Imaging: symmetrical masses with homogeneous contrast, no displacement of the pituitary stalk. Other clues for differential diagnosis with pituitary adenomas are with loss of posterior pituitary T1 high intensity, thickened stalk, pituitary symmetry, homogeneous enhancement, and parasellar dark signal intensity on T2-weighted [7]. Empty sella can be found as a late event in pituitary autoimmune disease [8].

The above mentioned characteristics are related to LH classical presentation. Nonetheless, there is a spectrum of autoimmune pituitary disease where isolate or multiple pituitary hormone deficiencies may have an autoimmune origin, based on studies assessing the presence of APA. Complement consumption test was the first method used to detect APA in a patient with Sheehan's Syndrome [9]. Currently, APA has been identified by different methods, including immunofluorescence [10], immunoblotting [11], and ELISA [12]. Hyperplastic and hypertrophic pituitary of women with breast cancer were used as a substrate for immunofluorescence in APA evaluation, with APA positivity in 12.6 % of patients with autoimmune endocrinopathies and without pituitary dysfunction [13, 14].

Kobayashi et al. [15] demonstrated that sera from patients with pituitary diseases reacted against an antigen of 22 kDa, extracted from rat pituitary, later identified by Takao et al. [16] as growth hormone (GH). At the same time, Crock et al. [17] described a specific immunoblotting for APA using human pituitary homogenate as antigen and positivity for APA was found in 70 % of confirmed LH cases, 55 % of suspected cases, 42 % in patients with Addison's disease, 20 % in patients with pituitary tumors,

15 % in cases with autoimmune thyroiditis, 13 % in rheumatoid arthritis and 9.8 % in controls. The antigen was identified as α-enolase, a pituitary protein of 49 kDa. The same authors also tested pituitary of monkeys, rats, and sheeps, finding similar results. Because APA positivity against α-enolase occurs in other conditions beyond LH, it cannot be considered a specific antigen [18].

Other antibodies against pituitary hormones have been identified: anti-TSH in the Graves' disease [19, 20], anti-FSH and LH in primary ovarian failure [21], anti-GH in idiopathic short stature [22] and in individuals with GH deficiency [23].

Using sulfur labeled radioligand assay to identify APA against GH and pituitary gland specific factor 1a (PGSF1a) and PGSF2, there were 36 % of positivity in patients with LH and hypopituitarism, 9.7 % in subjects with other autoimmune diseases and none in patients with pituitary adenomas [24].

In the search for more specific autoantigens, Lupi et al. [25] evaluated serum of 28 cases with LH (14 confirmed and 14 suspected), 48 patients with autoimmune thyroid diseases and 36 controls, using a panel of cytoplasmic proteins of human pituitary. The reactive bands were studied in a two-dimensional gel immunoblotting and mass spectrometry. A region between 25 and 27 kDa was positive more often amongst cases of hypophysitis, when compared to controls. This region contains two candidate antigens: a reading region of chromosome 14 (C14orf166) and chorionic somatomammotropin. This immunoblotting technique showed high specificity and sensitivity, compared to immunofluorescence against primate pituitary: 89 % vs 76 % and 64 % vs 57 %, respectively. More recently, GH and proopiomelanocortin were found as targets for autoantibodies in a patient with biopsy-proven IgG4-related hypophysitis [26].

Probably due to problems to obtain human pituitary, glands of several other animals were used as substrate. Primate pituitary glands, especially of young baboons, were successfully compared to the human pituitary, Immunofluorescence using frozen sections of young baboon pituitary, goat antibody conjugated against human immunoglobulins and fluorescein isothiocyanate was standardized by a De Bellis et al. [27]. APA evaluation using this technique was tested in patients with different idiopathic isolated and multiple hypopituitarism and data are compiled in Table 1.

On the other hand, Lupi et al. [38] assessing APA by immunofluorescence on section of primate pituitary glands, could not find a strict differentiation among pituitary autoimmune disease and other pituitary dysfunctions or

Table 1 Prevalence of APA in pituitary dysfunction

Condition studied	APA positivity	APA positivity % in other clinical conditions	Other autoimmune disease associated	Interesting note	References
Idiopathic GHD in 26 adults	33 %	2.8 % in 180 patients with other endocrine autoimmune diseases with GHD when tested			[28]
Idiopathic GHD in 26 children	27 %	23 % in 60 children with ISS and in 8 retested after 2 years, GHD was diagnosed			[29]
Hypogonadotrophic hypogonadism in 21 male adult	38 %	38.4 % in 13 patients with HH associated with other pituitary deficiencies	Personal and familial history of autoimmune disease associated to APA positivity		[30]
20 patients with Sheehan's syndrome	35 %			The pathogenic role for APA is debatable	[31]

Table 1 continued

Condition studied	APA positivity	APA positivity % in other clinical conditions	Other autoimmune disease associated	Interesting note	References
Idiopathic hyperprolactinemia in 66 individuals	25.7 %		Autoimmune disease and serum autoantibodies associated	Hypopituitarism (GHD and/or ACTH deficiency) in 6 among the 17 APA + individuals	[33]
Idiopathic hyperprolactinemia in 21 individuals	67.7%			Using ELISA method	[32]
Traumatic Brain Injury in 29 individuals followed-up for 3 years	44.8 %			Among 8 patients who developed hypopituitarism, 6 had APA +. The pathogenic role for APA is debatable	[34]
Repeated traumatic brain injury in 61 male boxers	23 %, being 11 boxers with hypopituitarism			Hypopituitarism was related to the presence of anti-hypothalamus antibodies but not to APA	[35]
Autoimmune polyendocrine syndromes	70.3 % in 199 patients with initial pituitary function normal, followed-up over 5 years. Hypopituitarism occurred in 18.8 % of APA positive patients but in none of the 50 patients with APA negative			Hypopituitarism only occurred in patients with APA positive in isolated pituitary cells. High APA titers were related to a minor cumulative survival	[36]
Idiopathic isolated hypopituitarism	15 % of 27 with ACTH deficiency, 26 % of 20 with GHD and 21 % of 19 with HH				[37]
Primary empty sella in 85 patients	6%			There was a positive correlation between APA + and pituitary dysfunction	[8]

ISS idiopathic short stature, *GHD* GH deficiency, *HH* hypogonadotropic hypogonadism, APA antipituitary antibody, + positivity

nonpituitary autoimmune diseases. Positivity for APA was found in 8 out of 16 histologically proven LAH (50 %), in 18 out of 291 pituitary adenomas (5.1 %), in 92 out of 707 patients with Hashimotos's thyroiditis (13 %), in 18 out of 254 patients with Graves' disease (7 %), in 5 out of 85 patients with empty sella (5.8 %), in 8 out of 30 patients with post-partum thyroiditis and in 3 out of 409 healthy controls (0.7 %). As APA was not specific or sensitive for LH, they created a score based on a data base with 304 cases of LAH and 98 pituitary adenomas with the following criteria: relation to pregnancy (if "yes": −4), pituitary mass volume (if ≥ 6 cm^3: +2) and symmetry (if asymmetric: +3), signal intensity (if medium or high: −1), signal homogeneity after gadolinium (if heterogeneous: +1), posterior pituitary bright spot presence (if lost: −2), stalk size (if enlarged: −5) and mucosal swelling (if present: 2). A score between −13 and +2 for LAH diagnosis and a score between −2 and +8 for pituitary adenoma had 92 % of sensitivity and 99 % of specificity.

The data described above reinforce the pleomorphic presentation of pituitary autoimmune disease. Therefore, therapeutic approach should be based on the grade of suspicious and clinical manifestations of LH. Hormonal replacement is the only approach indicated for hypopituitarism without mass effect. The replacement therapy should be periodically reassessed as spontaneous recovery of pituitary function, albeit rare, may occur. In the presence of headache, visual disturbances or other mass effects manifestations, the decision between an immunosuppressive therapeutic trial with glucocorticoids and/or azathioprine and surgery [39] with biopsy depends on clinical judgment. However, the precise diagnosis can only be obtained with histological assessment, once the current methods used for APA evaluation are not commercially

available and their specificity and sensitivity are not high enough to permit an accurate diagnosis.

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