

## INVITED REVIEW

## Lymphocytic hypophysitis: a rare or underestimated disease?

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### Abstract

Lymphocytic hypophysitis (LYH) is an uncommon autoimmune disease in which the pituitary gland is infiltrated by lymphocytes, plasma cells and macrophages and its function is usually impaired. It has to be suspected in pregnant women and in women with recent delivery presenting with hyperprolactinemia, headache, visual field alterations and changes of one or more pituitary hormone secretions with secondary impairment of related peripheral target glands, especially when associated with other autoimmune endocrine or non-endocrine disorders. It can also occur less frequently in prepubertal or post-menopausal women and in men.

Headache, visual field impairment and more rarely diplopia are due to extrasellar pituitary enlargement with optic chiasma compression and/or to invasion of cavernous sinuses. Among the 'isolated' pituitary hormone deficiencies, ACTH deficit is usually the earliest and most frequent hormonal impairment and in rare cases can induce an acute secondary hyposurrealism as the first sign of the disease, with high mortality in affected patients. Histopathological findings from pituitary biopsy show lymphoplasmacytic infiltrate with lymphoid aggregates surrounding atrophic acini of pituitary cells; immunohistochemical analysis shows numerous mast cells randomly distributed and also localized in the vicinity of capillaries, suggesting a possible influence on capillary permeability and angiogenesis, thus favoring the inflammatory and immunological aggression against pituitary cells. Nuclear magnetic resonance imaging shows uniform sellar floor depression and an extrasellar symmetrical pituitary enlargement, usually displacing the optic chiasma, which shows a rapid homogeneous enhancement after gadolinium also involving the adjacent dura (dural tail). Antipituitary antibodies have been detected in several patients with LYH but their role needs to be clarified. Since a possible spontaneous remission can occur, a careful follow-up is required in subclinical patients without important hyposurrealism or symptomatic extrasellar expansion. Medical (immunosuppressive, replacement and antiprolactinemic) and neurosurgical (decompression) treatments are needed in clinical symptomatic patients.

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### Introduction

Inflammatory processes of the hypophysis can be misdiagnosed because their clinical and radiological features mimic tumors in the sellar or parasellar region (1). They are classified as secondary when the inflammatory pituitary reaction is triggered by a definite etiologic infective agent or a known systemic disease, or primary when the inflammation is confined to the pituitary gland with no identifiable etiologic association (2).

Primary hypophysitis is histologically classified into three types (Table 1): lymphocytic hypophysitis (LYH), granulomatous hypophysitis (GRH), and xanthomatous hypophysitis (XH). It is unclear whether these are truly distinct entities or only different expressions of the same disease, since they share clinical and radiological features and can only be distinguished from each

other by histological examination. The characteristics of LYH will be clarified in the next sections. GRH is a granulomatous process involving the pituitary gland but not associated with other systemic chronic inflammatory diseases (3). The pathogenesis is still unclear: some authors suggest an autoimmune pathogenesis (4), others a viral etiology (5). GRH is characterized by pituitary infiltration of necrotizing granulomas that are formed by histiocytes and plasma cells surrounding areas of necrosis (2, 6–8). XH is an infiltrating process of the pituitary of unknown etiology consisting of foamy lipid-laden histiocytes with abundant clear cytoplasm and scattered lymphocytes (6, 9). Xanthogranulomatous hypophysitis (XGH) and necrotizing hypophysitis (NH) are classified by some authors as further autonomous entities of hypophysitis (10); the first (XGH) is the same as XH, reflecting only a variant terminology applied to xanthomatous

inflammation at numerous body sites; the second (NH) usually involves the posterior lobe and only occasionally the anterior lobe of the pituitary. The affected patients show distinct clinical and radiological features including characteristic diabetes insipidus (11). In this context, we consider lymphocytic hypophysitis and lymphocytic adenohypophysitis as one and the same, but indicate lymphocytic-infundibulo-neurohypophysitis as an infiltrative and inflammatory process involving the posterior lobe of the pituitary and the infundibulum (12). Finally, we consider lymphocytic-infundibulo-hypophysitis to be an inflammatory process involving the anterior and posterior hypophysis and the infundibulum (13). Secondary hypophysitis (Table 1) encompasses inflammatory pituitary processes during several systemic inflammatory diseases such as Takayasu's disease (14), Crohn's disease (15), Langerhans cell histiocytosis (16), Wegener's granulomatosis (17), sarcoidosis (18), inflammatory pseudotumor (19) or those caused by defined bacterial, fungal and viral agents, including HIV (20).

Among the primary hypophysitis diseases described here we focus on LYH to clarify some ambiguous aspects of the disease which can contribute to misdiagnosis; lymphocytic-infundibulo-neurohypophysitis and lymphocytic-infundibulo-hypophysitis are usually easy to diagnose because of the concomitant partial or total diabetes insipidus and the characteristics at magnetic resonance imaging (MRI) (loss of post pituitary 'bright spot', see below).

## Lymphocytic hypophysitis

Lymphocytic infiltration of endocrine glands, including the pituitary, does not always cause endocrine dysfunction since it can be observed at autopsies of patients who did not show functional alterations of the affected glands when they were alive (21–23). Panhypopituitarism due to lymphoplasmacytic pituitary infiltration was described by Rapp and Pashkis in 1953 (24) but they could not classify this disorder as autoimmune

because the concept of endocrine autoimmunity was introduced some years later (25) for Hashimoto's thyroiditis, due to the coexistence in affected patients of lymphocytic thyroid infiltration and plasma thyroid autoantibodies. After the classification of Hashimoto's thyroiditis as an autoimmune endocrine disease, an autoimmune pathogenesis for LYH was suggested for the first time by Goudie and Pinkerton (26). They described the occurrence of post-partum amenorrhea and hypothyroidism in a young woman who subsequently died from severe acute secondary hyposurrealism after appendectomy. The autopsy revealed massive lymphoplasmacytic infiltration of both the pituitary and thyroid glands and adrenal atrophy (26). After this first description (26) and before the introduction of pituitary biopsy and of MRI as diagnostic procedures, very few cases had been described in the literature (about 30 cases up to 1990) (5, 27–30). These were diagnosed on the basis of autoptical or post-hypophysectomy histopathological findings. Over the last 13 years the number of diagnosed cases has increased considerably, due probably to improved imaging criteria (31, 32), and over 200 cases have been diagnosed by 2003, considering only those cases where the inflammatory process involved only the anterior lobe of the pituitary, without affecting the posterior lobe (2, 3, 13, 31–64).

## Clinics and imaging of LYH

An exhaustive review of the literature (34, 51) shows that women are affected more frequently than men with a ratio of about 5:1 (34) or 8:1 (51). The mean age at diagnosis is estimated as being 34.5 years for women and 44.7 years for men, although prepubertal (42, 65) or elderly cases have also been described (36, 53). LYH is rare in the Japanese population, but not in Caucasians with a Caucasian to Japanese ratio of about 3:1. However, although this assumption is based on the study of a large cohort of patients (38), it awaits epidemiologic confirmation to avoid a bias of case reporting. LYH seems to be strongly correlated with pregnancy, especially in the first large series of patients reported in the literature (34, 38). Usually, the first trimester of pregnancy is spared. Instead, LYH frequently affects women in the last six months of pregnancy and in the first six months after delivery (34, 38). However, in recent years reports of LYH cases occurring outside pregnancy have been on the increase. This suggests a higher prevalence than previously thought (12, 51, 59–64). Usually, the affected patients have a family or their own history of autoimmunity. The most frequently described allele in the few patients in whom the study has been performed is HLA DR4, but HLA DR5 has also been found (38) (Table 2).

At the onset of the disease patients present symptoms and signs of extrasellar pituitary enlargement and only

**Table 1** Classification of hypophysitis.

<b>Primary</b>
Lymphocytic hypophysitis
Granulomatous hypophysitis
Xanthomatous hypophysitis
<b>Secondary</b>
Systemic disease
Takayasu's disease
Crohn's disease
Langerhans cell histiocytosis
Sarcoidosis
Inflammatory pseudotumor
Infective etiology
Bacterial
Viral
Fungal

**Table 2** General characteristics of lymphocytic hypophysitis.

Sex: F/M 8/1
Mean age at start of disease: 34.5 (F)–44.7 (M)
Race: Caucasian/Japanese 3/1
Correlation with pregnancy: frequent appearance from 6 months before to 6 months after delivery
Familial or personal history of autoimmunity
HLA apotype: HLA DR4 (44%); HLA DR5 (23%)

later do features of hypopituitarism become apparent (Table 3). Thus, headache is the first symptom. This usually precedes or is coupled with visual field impairment and, more rarely, diplopia due respectively to compression of the chiasma or invasion of cavernous sinuses by an enlarged pituitary mass (38). Hyperprolactinemia affects approximately one third of patients, causing amenorrhea/galactorrhea in women (39) and sexual dysfunction in men (65). However, it is underestimated in pregnant women and in women with recent delivery, whereas it is frequently ascribed to prolactinomas when occurring in men or in women outside of pregnancy (51, 60, 66, 67). Several causes have been suggested to explain hyperprolactinemia in LYH. Bottazzo *et al.* in 1975 (68) found autoantibodies to prolactin-secreting cells, suggesting a putative stimulating effect of these antibodies, but this assumption was not confirmed. Probably a multifactorial etiology related to the diffuse inflammatory process can be evoked for the hyperprolactinemia, 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 (1). Some patients with LYH can, however, present with hypoprolactinemia (32). Usually partial or total hypopituitarism is associated with alterations of prolactin secretion, even if pituitary function can be normal in some cases (69, 70). Thus, when LYH is suspected, basal and dynamic hormonal pituitary secretions have to be studied to disclose subclinical or overt alterations.

**Table 3** Symptoms and signs of lymphocytic hypophysitis.

1. Related to the pituitary enlargement
Headache (60%)
Visual field impairment (40%)
More rarely diplopia
2. Related to pituitary secretion alterations
Unusually normal pituitary function
Hyperprolactinemia (30%)
More rarely hypoprolactinemia
Subclinical hypopituitarism (25%)
ACTH deficiency (the earliest and most frequent isolated pituitary deficiency)
Rarely acute hyposurrealism with high mortality
Hypogonadotropic hypogonadism (usually diagnosed only in males)
Rarely isolated GH deficiency

Among the 'isolated' pituitary hormone deficiencies, adrenocorticotropin (ACTH) deficiency is the earliest and most frequent alteration in patients with LYH. This is present in about 65% of cases (32); in rare cases it can induce acute secondary hyposurrealism as the first appearance of the disease, with high mortality of affected patients (27, 71). LYH can also cause thyrotropin (TSH) and/or gonadotropin deficiencies (which are usually misdiagnosed when LYH affects women in pregnancy or in the postpartum period) whereas data on the effects on growth hormone/insulin-like growth factor-I (GH/IGF-I) secretions are scarce and inconclusive (38). A hypopituitarism involving almost all hormones usually occurs when the inflammatory process induces pituitary tissue destruction (38) (Table 3).

Imaging of LYH is particularly important to differentiate it from tumors in the sellar or parasellar region even if this is not always possible. X-ray, but mostly MRI, are useful for this purpose (Table 4). Radiographs reveal a usually flat sellar floor in LYH, but a unilaterally depressed one in pituitary adenomas. MRI has considerably improved the diagnostic accuracy of LYH by differentiating it from pituitary tumors (13, 31, 57, 70, 72). In fact, at MRI, patients with LYH show an enlarged pituitary with a symmetrical sovrasellar extension which displaces the optic chiasma (Fig. 1A,B), whereas patients with adenoma show asymmetrical pituitary enlargement with deviation of the stalk; the stalk is thickened but not usually deviated in LYH (31). The pituitary enhancement after injection of gadolinium is homogeneously intense in LYH and shows a strip of enhanced tissue along the dura madre (the so-called 'dural tail') (Fig. 1B,C); the enhancement can also involve the arachnoid (31). Patients with adenomas, on the other hand, show delayed and poor enhancement usually without a 'dural tail' after gadolinium. If the autoimmune process also involves the infundibulum and the neurohypophysis, causing a lymphocytic-infundibulo-hypophysitis or an infundibulo-neurohypophysitis, there is a loss of the 'bright spot'. Diabetes insipidus is usually present. In rare cases an empty sella can represent an unusual feature of LYH at MRI (72).

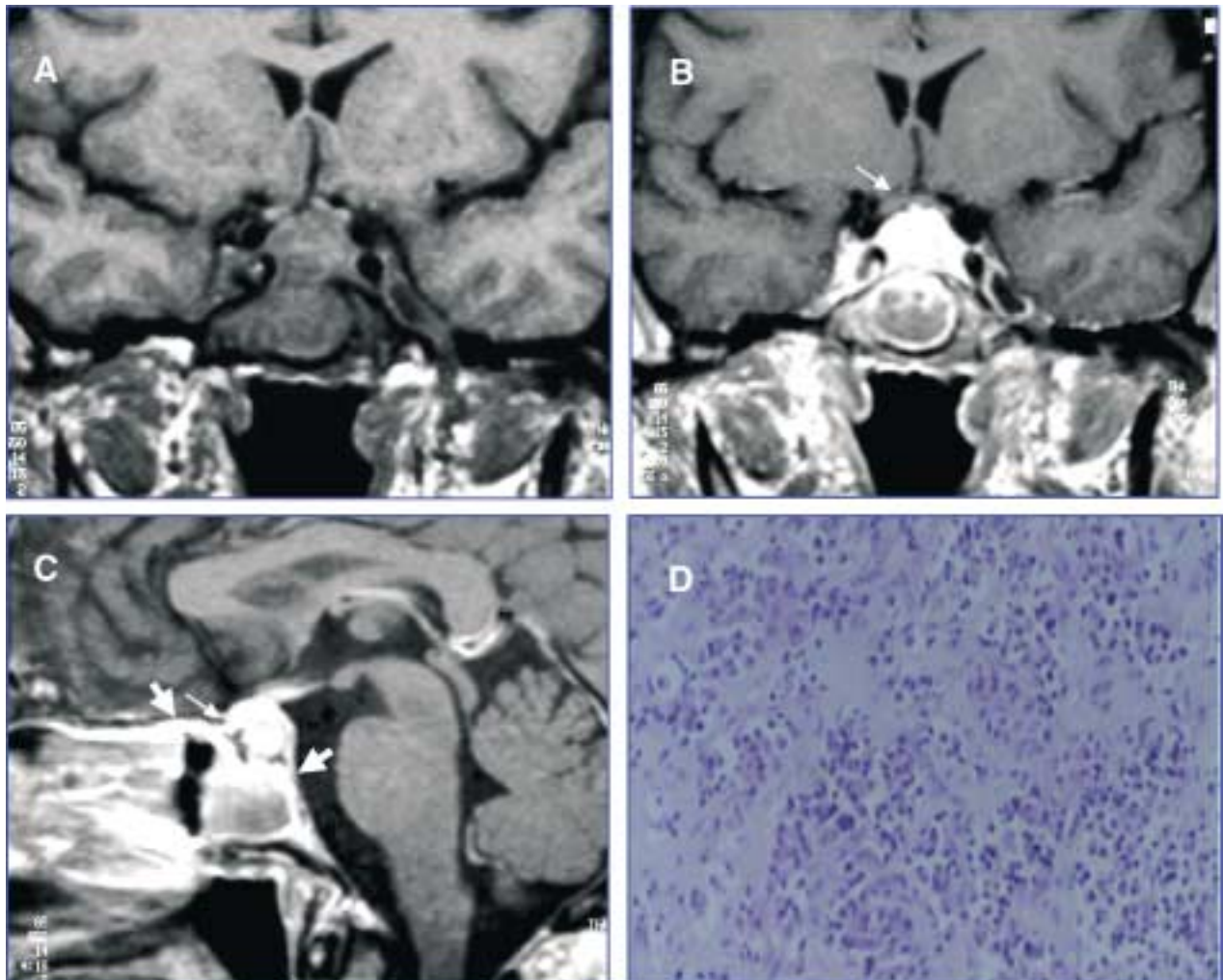
Despite the schematic criteria to differentiate LYH from pituitary adenoma described above and summarized in Table 4, findings from imaging tend to overlap. For this reason histopathological findings from pituitary biopsy remain the gold standard for diagnosing LYH (see next paragraph).

### **Etiopathogenesis**

Although there is still some debate, an autoimmune pathogenesis is suggested by several histopathological, laboratory and clinical findings. The first histopathological observations were usually derived from autopsical or post-surgical pituitary examinations, whereas in more

**Table 4** Differences between lymphocytic hypophysitis (LYH) and pituitary adenoma using different imaging techniques.

Imaging technique	LYH	Adenoma
Sellar X-Ray	Sellar floor uniformly flat	Unilateral depression of sellar floor
Pituitary NMR	Pituitary enlargement with symmetrical sovrasellar expansion	Unilateral endosellar mass (microadenoma) or inhomogeneously expanding pituitary mass with asymmetrical sovrasellar extension (macroadenoma)
	Compression and displacement of chiasma	Contralateral deviation of stalk
	Stalk thickened but not deviated	Slight, delayed and inhomogeneous enhancement
After gadolinium	Intense and homogeneous enhancement of pituitary mass	Usually lack of 'dural tail'
	Appearance of 'dural tail'	Persistence of 'bright spot'
	Loss of 'bright spot' of neurohypophysis if diabetes insipidus is associated	



**Figure 1** Radiological appearance on magnetic resonance (A, B, C) and histopathological findings (D) of lymphocytic hypophysitis. (Courtesy of Prof. Sossio Cirillo, Professor of Neuroradiology, Department of Neurological Science, 2nd University of Naples). Coronal precontrast (A) and postcontrast (B) T1-weighted images show a homogeneous pituitary mass with symmetrical sovrasellar extension compressing the optic chiasma (arrow in B). Coronal (B) and sagittal (C) postcontrast images show homogeneous enhancement of the pituitary mass, stalk, which appears thickened (thin arrow in C), and adjacent meningeal structures (thick arrows in C). (D) Lymphoplasmacytic aggregates surrounding atrophic acini of pituitary cells.

recent reports, specimens have been obtained by trans-sphenoidal pituitary biopsy which is thought to be the gold diagnostic standard for LYH.

The histopathological aspects are similar to those described for other endocrine glands involved in autoimmune processes (73, 74). In fact, the adenohypophysis is extensively infiltrated by lymphoplasmacytic cells, consisting of lymphocytes, plasma cells and macrophages (Fig 1D). T lymphocytes (of CD4 rather than CD8 class) are significantly more numerous than B lymphocytes (34, 38) and are sometimes arranged in lymphoid follicles with a germinal center. Lymphoplasmacytic aggregates surround atrophic acini of pituitary cells (51), whereas the remaining pituitary tissue shows areas of reactive fibrosis (51, 69, 75), but neither granulomas nor xanthomas (51, 76) are present. Immunohistochemical analysis shows numerous mast cells (77) and residual pituitary cells still containing the corresponding hormones (65). Mast cells are randomly distributed and also localized in the vicinity of capillaries. This could favor capillary permeability and angiogenesis, influencing the inflammatory and immunological aggression to pituitary cells (77). Although several autoimmune diseases are correlated to particular HLA alleles (78), HLA has been typed in a small sample of patients with LYH. The results are inconclusive. In fact, in 17 patients studied the predominant allele was the HLA DR4, followed less frequently by HLA DR5 (38). However, in none of the patients studied did the pituitary cells express inappropriate HLA class II molecules (79) which have often been expressed in tissues affected by autoimmunity (80, 81).

The role of antipituitary antibodies (APAs) in LYH has yet to be clarified but their detection has amplified the diagnostic criteria, also suggesting a possible pathogenetic role. The methods used for detection have been the complement consumption test, immunofluorescence, immunoblotting, and radioligand assay.

The complement consumption test was the first method employed to detect pituitary autoantibodies (82). Testing against homogenates of human adenohypophysis plasma samples drawn during pregnancy, at delivery and in the immediate post-partum period from a large cohort of normal pregnant women, the authors detected antipituitary antibodies but only in the sera of 18% of women studied in the first week after delivery, of whom 25% proceeded towards pituitary insufficiency. In contrast, only 4% of women negative for antipituitary autoantibodies showed progression to pituitary insufficiency (82). However, following this report the method has not been employed by other laboratories.

The immunofluorescence method is one of the most widely used methods to detect pituitary autoantibodies (28, 68, 83–87). Both human and animal pituitaries can be used as sources of tissue in which to detect APAs by this method. In the beginning, pituitaries were obtained from fetuses or corpses or after

therapeutic hypophysectomy. Subsequently, presumably because of legal difficulties, several authors have had good results with pituitary glands from animals, in particular primates, guinea pigs or rats. Usually the animals undergo castration and thyroidectomy some weeks before pituitary ablation. Excellent results have been obtained using pituitaries from guinea pigs or rats (27). Results comparable to those obtained when using human glands have been reported by some authors employing pituitaries from primates (88), in particular from young baboons (87). Structurally, pituitary autoantigens are mostly lipoproteins and are located, like other endocrine autoantigens, in the intracellular membrane of the endoplasmic reticulum. The introduction of the four-layer immunofluorescence technique allowed investigators to identify autoantibodies reacting to several hormone-secreting pituitary cells (68). Using this technique, the same pituitary section is tested consecutively against the patient's serum and the animal hormone antiserum. The different color of anti-Ig conjugate against the human serum and against the animal serum, respectively green (FITC) and red (rhodamine), allows direct visual assessment of whether the patient's serum and the animal's anti-hormone serum stain the same or different pituitary cells. Since the two sera are directed against different antigens, the immunofluorescence produced by the patient's autoantibodies is not prevented by the hormone antiserum and vice versa. This is confirmed by the lack of variation of cytoplasmic staining when human positive serum is preabsorbed with an excess of the appropriate hormone (83). Screening a cohort of autoimmune polyendocrine patients, Bottazzo *et al.* first detected antipituitary autoantibodies (68) using as substrate sections of human pituitaries obtained surgically by hypophysectomy from patients with breast cancer, whose pituitary is markedly hypertrophic and hyperplastic. They showed a positive immunoreactivity in 12% of sera investigated involving only a confined group of pituitary cells. These have subsequently been recognized as prolactin (PRL)-secreting cells by a four-layer immunofluorescence technique (68). These antibodies belonged to the class of IgM but in most cases also to classes IgG and IgA. When the same technique was used on a larger series of patients, the same and other authors (28, 89–92) confirmed the detection of PRL-cell antibodies, mainly in patients with autoimmune polyendocrinopathies (about 12.6% of 420 patients tested) and with lower prevalence in patients with single autoimmune endocrinopathies (2.3% of 587 patients tested) except for patients with autoimmune hypoparathyroidism (92), who showed the highest prevalence of PRL-cell autoantibodies (about 23.3% of 86 patients tested). None of the patients positive for PRL-cell autoantibodies showed clinical signs of pituitary dysfunction. However, a potential pathogenetic role of these antibodies in autoimmune hypophysitis seems to be suggested by a report

regarding a woman with Addison's disease: the presence of PRL-cell antibodies without alterations of pituitary function when she was alive, but with histopathological findings of adenohypophysitis (pituitary lymphoplasmacytic infiltration) at post-mortem autopsy (90) seem to indicate that these antibodies could play a pathogenetic role in the initial (subclinical) stage of autoimmune aggression. Even if PRL-cell autoantibodies were the first to be detected by immunofluorescence, antibodies to other pituitary hormone-producing cells were subsequently detected. In particular, antibodies to ACTH-secreting cells were detected in some patients with isolated ACTH deficiency (29, 93) and in 25% of patients with Cushing's disease (85). In these latter patients, they seem to favor the relapse of pituitary tumor, suggesting a stimulating action on the ACTH-secreting cells in Cushing's disease (85). On the contrary, in patients with ACTH deficiency, ACTH-cell autoantibodies seem to be directed against a 70 kDa enzyme, aspartil protease, which catalyzes the conversion of proopiomelanocortin to ACTH (93) even if in these patients autoantibodies directed to the surface of pituitary cell lines have also been detected (94).

Autoantibodies to GH-secreting cells were first detected by Bottazzo *et al.* (84) in a patient with Turner's syndrome, partial GH deficiency and a familial history of autoimmune polyendocrinopathy (Schmidt's syndrome in the mother). These antibodies have also been detected in only three out of 397 prepubertal subjects with idiopathic short stature (29) and in one out of four patients with idiopathic GH deficiency (28). Thus their role in these disorders still has to be clarified.

Autoantibodies staining all the cells from animal pituitary cells were detected in patients with Sheehan's syndrome (28), in some patients with type 1 diabetes mellitus (86, 91) and in some of their relatives free from disease (91). However, none of the APA-positive diabetic patients had altered pituitary function (86, 91). Antipituitary antibodies directed against a 49-kDa autoantigen in patients with Sheehan's syndrome have recently been confirmed. This suggests that pituitary autoimmunity may play a pathogenetic role in the hypopituitarism following postpartum hemorrhage (95), even taking into account the fact that pituitary autoantibodies can be the result of antigen exposure following pituitary necrosis rather than being the cause of pituitary impairment.

The immunoblotting method introduced by Crock *et al.* in 1990 (96) is a specific method to detect antipituitary antibodies. They tested the sera of some patients with idiopathic or secondary GH deficiency and some normal subjects against cytosolic and membrane autoantigens prepared from post-mortem human pituitaries. One of 19 patients with idiopathic GH deficiency precipitated a 45-kDa membrane protein, an antigen thought to be pituitary specific, and another precipitated a 43-kDa cytosol protein, an antigen diffusely represented in the brain. Among patients

with acquired GH deficiency, one out of 14 showed autoantibodies to a 45-kDa antigen while three showed antibodies to a 95-kDa membrane protein. None of the sera from the control group was positive (96, 97). The same authors lent further support to the hypothesis of an autoimmune pathogenesis of LYH, studying a large cohort of biopsy-proven or suspected patients with this disease. They found a high prevalence (70%) of precipitation against a 49-kDa cytosolic protein in sera from patients with biopsy-proven LYH and a lower but nevertheless significant prevalence (55%) in sera from patients with suspected LYH. However, the same precipitation was observed in 10% of controls, in 15% of patients with thyroid autoimmunity, in 42% of patients with Addison's disease and in 13% of those with rheumatoid arthritis (98). Moreover, 50% of sera from patients with biopsy-proven LYH and 30% of sera from those with suspected LYH precipitated another autoantigen, a 40-kDa cytosolic protein, also precipitated by 10% of the sera from controls but by none of the sera from patients with pituitary tumors or other autoimmune diseases. Immunoprecipitation against the 49-kDa protein was also observed in two out of three studied patients with isolated ACTH deficiency. Since an ACTH deficiency frequently occurs at an early stage of LYH, because ACTH-secreting cells are the first ones damaged by the inflammatory process, the authors suggested that the 49-kDa antigen may be released by these damaged cells, thus evoking the immune response with production of the corresponding autoantibodies. In light of this they concluded that although this antigen is not specific because it is present in several tissues of different species, it can be considered an important serological marker of autoimmunity both for isolated ACTH deficiency and for LYH (98). In a more recent paper, the 49-kDa autoantigen associated with LYH was purified and identified as alpha-enolase (99). The autoantigen was purified from monkey brain and human placental cytosol. Limited amino acid sequencing after proteolytic digestion of the human placental protein showed identity with alpha-enolase. The identification was confirmed using sera from patients with pituitary autoimmunity, which strongly reacted with recombinant human alpha-enolase, indicating that the immunoreactive epitopes are largely conserved from yeast to human. The authors concluded that alpha-enolase, even if not specific for pituitary but widely represented in human and animal tissues, is the first autoantigen isolated in LYH (99). It can be considered one of the targets of APAs, in the same way that 21-hydroxylase can be identified as one of the targets of adrenocortical autoantibodies in autoimmune Addison's disease (87, 100). Moreover, gamma-enolase, an enolase subunit known as neuron-specific enolase (NSE) and normally expressed in the pituitary, has also recently been demonstrated in the placenta (101). In fact, sera from patients with

LYH reacted with both pituitary and placental NSE (i.e. gamma-enolase). The autoimmune response evoked by an antigen shared between the pituitary and the placenta seems to provide a theoretical basis for the strong predilection of LYH to occur during or after pregnancy (101).

On the other hand, pituitary autoantibodies against a 22-kDa antigen from porcine pituitary have been detected in 57% of patients with type 1 and in 24% of patients with type 2 diabetes mellitus without LYH (102). Thus, concerning the clinical significance, probably some APAs can be harmless, whereas others can activate intracellular signaling and exert a biological function (87, 103).

Autoantibodies against some pituitary hormones have been detected in several conditions (104–109). In particular, antibodies against TSH in patients with Graves' disease (104, 105), against follicle-stimulating hormone and luteinizing hormone (LH) in patients with premature ovarian failure (106), against GH in patients with short stature (107) and in those with GH deficiency (108), against alpha-melanocyte-stimulating hormone (MSH), ACTH and LH releasing hormone in patients with anorexia or bulimia nervosa (109) have been detected but their pathological significance remains to be seen.

The radioligand assay is a method recently employed in patients with LYH to investigate the presence of autoantibodies against three specific pituitary proteins, GH and two novel pituitary-specific proteins, namely pituitary gland specific factor 1a (PGSF1a) and 2 (PGSF2) (110). The presence of each antibody was studied by radioligand assay, using human S-labeled protein. Eighteen percent of patients with LYH with

pituitary enlargement, 36% of patients with hypopituitarism without pituitary enlargement and 9.7% of patients with other autoimmune disease, but no patients with non-functioning pituitary adenoma, were positive for one or more of the antibodies studied, suggesting that the detection of these antibodies may be useful for the diagnosis of LYH (110).

Another argument advanced in favor of the autoimmune pathogenesis of LYH is the frequent association with other endocrine or non-endocrine autoimmune diseases. The most common association with endocrine autoimmune disease is with Hashimoto's thyroiditis or Graves' disease (111), but other described associations are with type 2 diabetes mellitus, Addison's disease, parathyroiditis, pernicious anemia, and chronic atrophic gastritis (55, 65, 112). Less frequently, LYH has been described as associated with lupus erythematosus (35, 49), erythema nodosum (48), germinoma (41), dacryoadenitis (43), idiopathic retroperitoneal fibrosis (113), asymptomatic primary biliary cirrhosis (36), and autoimmune polyglandular syndrome (APS) type 1 (48, 114) or, more frequently, type 3a (73, 74, 87) (Fig. 2).

The natural history of LYH is also similar to other autoimmune endocrine diseases (73, 115), progressing through several stages (5, 73) in which the different histopathological features are paralleled with corresponding clinical aspects. At disease onset the pituitary gland is enlarged, edematous and with lymphocytic infiltration, putting pressure on adjacent structures. This leads to headache, visual field impairment and, more rarely, diplopia. At this stage a sub-clinical hypopituitarism can be present and may be disclosed with appropriate dynamic studies but a spontaneous

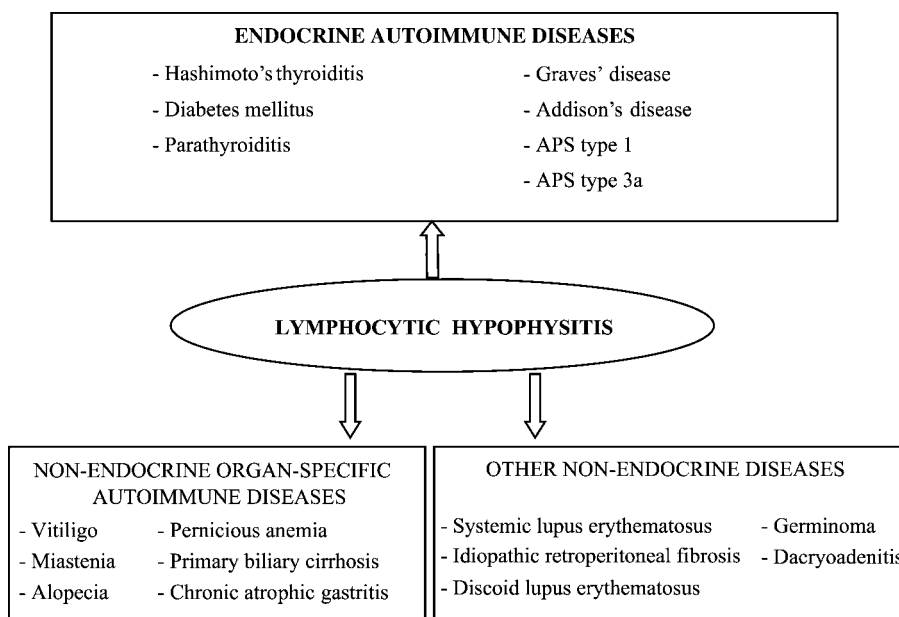


Figure 2 Lymphocytic hypophysitis can be associated with autoimmune endocrine and non-endocrine diseases.

remission can occur if the pituitary tissue is not destroyed. In a subsequent stage, the pituitary parenchyma, destroyed by the inflammatory process, is substituted with fibrous tissue, progressing sometimes to atrophy. At this stage, symptoms of partial or total hypopituitarism usually appear (5). In conclusion, a putative autoimmune pathogenetic mechanism can be hypothesized taking into account the interrelationships between the hypothalamic–pituitary–adrenal (HPA) axis and the mediators of inflammatory process evoked by the autoimmune aggression (21, 116, 117) (Fig. 3). Usually, in the course of the immune inflammatory process, some cytokines produced at inflammatory sites stimulate the HPA axis leading to its hyperactivation, which contributes to the extinction of the same inflammatory process. In fact, corticotropin releasing hormone (CRH) together with arginine vasopressin (AVP) induce the release of pituitary ACTH which stimulates cortisol secretion from the adrenal gland. AVP can also directly stimulate cortisol production by the adrenal gland, via V3 receptors (117). Cortisol exerts an inhibiting action on the inflammatory and immune processes. For this reason both AVP and ACTH can be considered neurohormones influencing both immune and inflammatory processes (118).

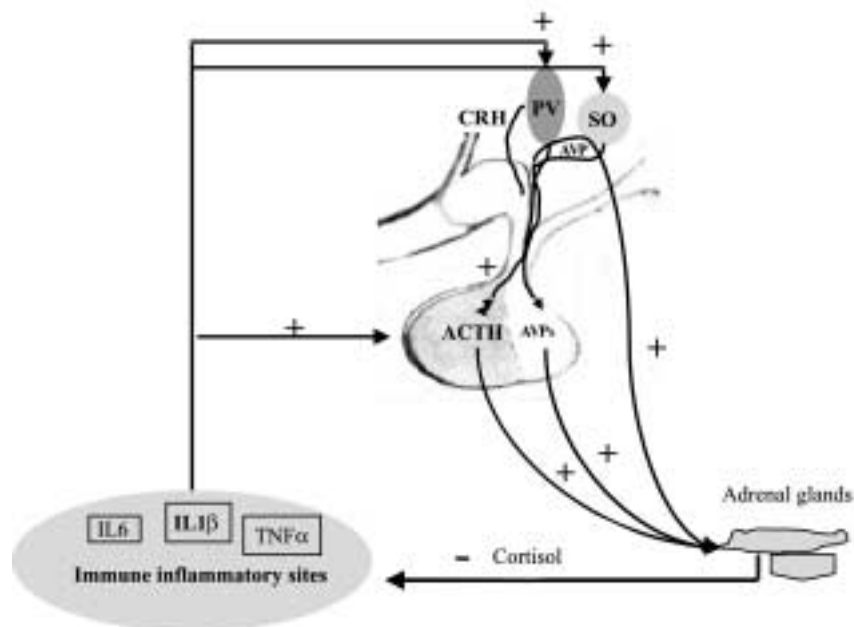
The disruption of the cytokine–HPA axis circuit can predispose to autoimmunity (119). In LYH when the immune aggression causes important damage to the pituitary cells, mostly ACTH-secreting cells in

the early stage, the secondary reduced secretion of cortisol is not able to interrupt the immune process, thus perpetuating its aggression to pituitary cells with consequent stable pituitary dysfunction.

When the cell damage is transient because it is related mostly to the pituitary edema, the rapid normalization of the pituitary–adrenal axis secretion interrupts the immune inflammatory process inducing spontaneous recovery of pituitary function. Conversely, when the immune inflammatory process also involves the hypothalamus and neurohypophysis, cortisol secretion is highly impaired, due to the lack of both ACTH and AVP stimuli. If this aggression is massive it can induce a precocious adrenal atrophy which could explain the rare cases where an acute secondary hypoadrenalism can occur as the first appearance of the disease, with high mortality in affected patients (29, 71).

### Diagnosis of LYH

The gold standard for the diagnosis of LYH in patients with the above-described clinical symptoms is a histopathological study by pituitary biopsy showing the peculiar lymphoplasmacytic infiltration. However, NMR imaging and detection of antipituitary antibodies have improved the diagnostic procedures allowing LYH detection at a subclinical stage in patients with other autoimmune diseases or with apparently



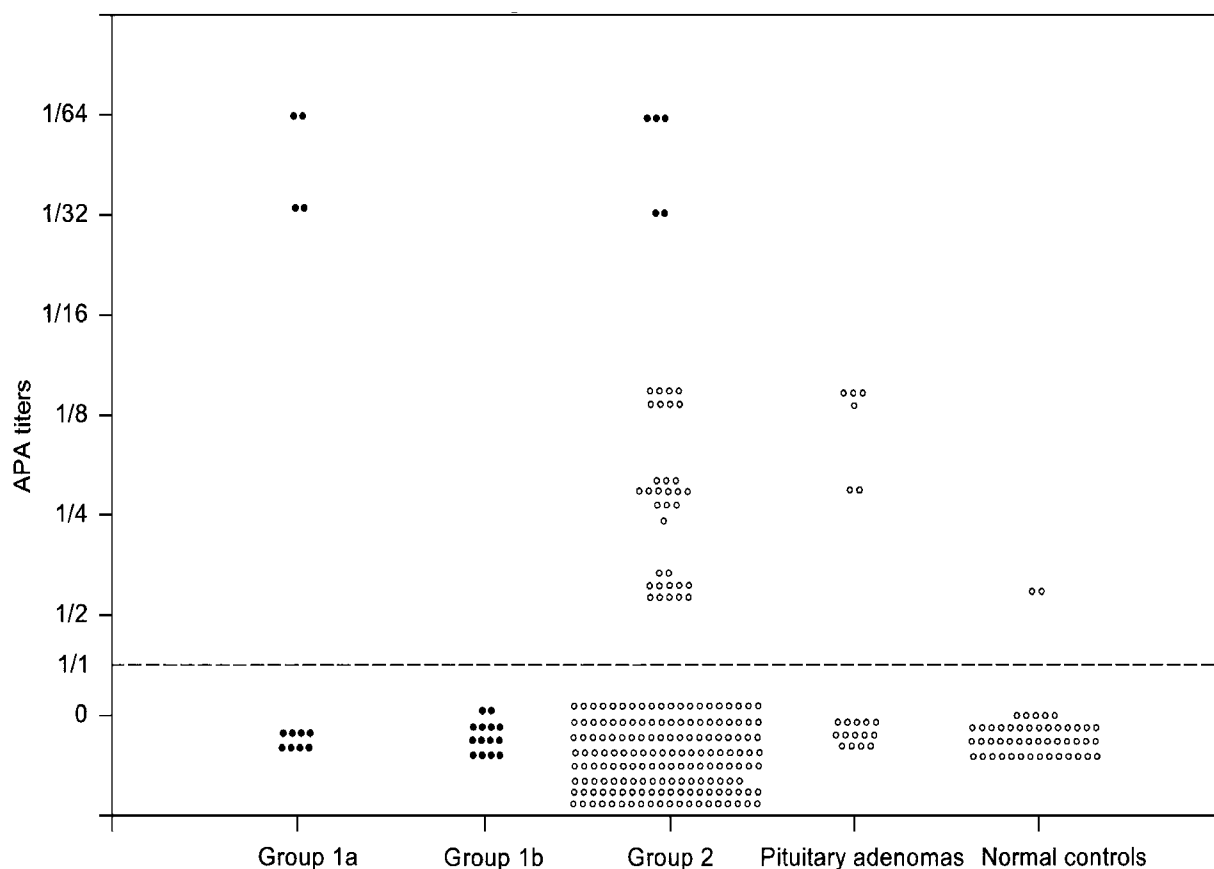
**Figure 3** Reciprocal interrelationships between AVP, CRH–ACTH–cortisol axis and cytokines released from immune inflammatory sites. Cytokines released from inflammatory sites stimulate hypothalamic CRH and probably also AVP. CRH, together with AVP, induces the release of pituitary ACTH, which stimulates cortisol secretion from the adrenal gland. Cortisol, whose secretion can also be directly stimulated by AVP, dampens the inflammatory response by inhibiting cytokine production. PV, paraventricular nucleus; SO, supraoptic nucleus; AVPs, AVP storage in post-pituitary; IL-6, interleukin 6; IL-1b, interleukin 1b; TNF $\alpha$ , tumor necrosis factor  $\alpha$ .

idiopathic pituitary dysfunctions. Since ACTH-secreting cells seem to be the first pituitary cells damaged by the autoimmune inflammatory process, several authors have looked for the presence of antipituitary antibodies both in isolated ACTH deficiency and in LYH, also indicating their possible diagnostic and/or pathogenetic role (27, 93, 98). On the other hand, the occurrence of pituitary autoantibodies and their role in patients with idiopathic GH deficiency is still discussed (28, 96, 108, 110, 120). As previously reported, Crock *et al.*, testing the sera of some patients with idiopathic or secondary GH deficiency against cytosol and membrane autoantigens, detected antibodies to such antigens not only in two out of 19 patients with idiopathic GH deficiency, but also in four out of 14 patients with acquired GH deficiency (96).

Following our studies on GH-deficiency (GHD) in adults (121–123) we used an immunofluorescence method to investigate the presence of APAs in adults with apparently idiopathic GHD and in patients with acquired GHD in order to verify the prevalence of pituitary autoimmunity in these patients. Moreover, we studied 180 patients with organ-specific autoimmune

diseases to evaluate the prevalence of APA-positive patients and to correlate the presence of APAs to their pituitary functional state and particularly to GH secretion (87).

APAs were found at high titers in four of 12 patients with apparently idiopathic GHD but in none of the patients with acquired GHD. APAs were also found in 40 of 180 patients with autoimmune organ-specific diseases (22.2%), 35 of them at low titers (87.5%), and five at high titers (12.5%). Autoimmune APA-negative patients and all APA-positive patients at low titers had normal pituitary function, whereas all APA-positive patients at high titers had a severe isolated GHD (Fig. 4). With respect to the characteristics of the hypothalamus and sellar regions, among the five autoimmune patients positive for APA at high titers, three showed normal imaging, one showed imaging suggestive of infundibulo-hypophysitis (pituitary enlargement with enhancement after gadolinium, pituitary stalk thickening and absence of bright spot) and another had a partial empty sella, which can be an unusual feature of LYH at MRI (72). Our results suggest that APAs, when detected at high titers, are



**Figure 4** Behavior of APAs in adults with childhood-onset idiopathic GH deficiency (group 1a) and adults with GHD secondary to surgery for pituitary and parasellar tumor (group 1b), patients with autoimmune endocrine disease (group 2), patients with pituitary adenomas and normal controls. The black circles indicate patients with GHD diagnosed by impaired response to insulin tolerance test and arginine test. From De Bellis *et al.* (87) with permission from Evelyn M Frazier, Journals Coordinator of the Endocrine Society.

a good diagnostic tool to reveal the occurrence of GHD in adults with autoimmune endocrine diseases. Moreover, they may indicate an autoimmune pituitary involvement in adults with apparently idiopathic GHD, suggesting that the prevalence of autoimmune GHD is much higher than that so far considered (87).

### Therapeutic strategy

The natural history of LYH indicates that it can evolve in different ways, thus requiring different therapeutic strategies. Since a possible spontaneous remission can occur (42, 124–127) a careful follow-up is advisable in subclinical patients without important hyposurrealism nor symptomatic extrasellar expansion. Surgical transsphenoidal treatment, with an intrasurgical cryostatic slide to confirm diagnosis and to save possible viable pituitary tissue, is required in patients with symptoms and/or signs of severe compression (61, 81). In some cases pituitary biopsy is both diagnostic and therapeutic, because after this procedure a progressive recovery of pituitary function can be observed (2).

Glucocorticoids or other anti-inflammatory and immunosuppressive (methotrexate, cyclosporin A) drugs have been suggested as medical treatment but their long-term efficacy still needs to be confirmed. High-dose methylprednisolone pulse therapy seems to be effective in about 30% of treated patients (128). Recently, a young woman suffering from severe visual disturbance 3 months after delivery was diagnosed as having an LYH. Her MRI revealed a pituitary mass with an extension into the suprasellar cistern, with intense and homogeneous enhancement after gadolinium. She was treated with high-dose methylprednisolone pulse therapy (64). Her visual disturbance dramatically ameliorated on the first day of treatment and MRI revealed marked mass reduction, whereas pituitary function completely recovered 6 months after therapy (64).

Positive results have also been reported using cyclosporin A in a patient with LYH and APS type 1 (48). Bromocriptine, a dopamine agonist, can improve visual field alterations and lower hyperprolactinemia but the beneficial impact of this agent on the course of the disease is unproven (2). Stable hypopituitarism in the course of LYH or due to the neurosurgical therapy has to be appropriately corrected with replacement hormone therapy. Finally, data on the so-called 'isohormonal therapy', whose effectiveness in restoring some hormonal subclinical dysfunction in other autoimmune endocrine diseases has been demonstrated (129–132), are lacking in LYH. Such therapy utilizes hormonal products of the gland affected by the immune process to influence this process at the preclinical stage, when the affected gland is not completely and irreversibly destroyed, and it may act by feedback inhibition of glandular function or by determining suppression of

autoimmunity or by a combination of both mechanisms (130, 133). A longitudinal study of patients positive for APAs treated at the stage of subclinical hypopituitarism could be useful to clarify this aspect.

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