Pituitary antibodies and lymphocytic hypophysitis

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Lymphocytic hypophysitis (LYH) is a pituitary disease which can cause headache, changes in visual field and pituitary dysfunction. The clinical, histopathological and morphological findings and its association with other autoimmune disorders allow LYH to be included among the autoimmune diseases. Pituitary trans-sphenoidal biopsy is thought to be the diagnostic gold standard for LYH, even if some morphological findings on hypothalamic–pituitary magnetic resonance imaging (MRI) can suggest the occurrence of this disease. Despite the fact that organ-specific antibodies are good markers of many autoimmune endocrine diseases, the pathogenetic and diagnostic roles of anti-pituitary antibodies (APAs) in LYH are still under discussion. In fact, several methods have been used to detect APAs, but the conflicting results from different methods have impaired the clinical relevance of these antibodies. Recently, APAs have been detected by an immunofluorescence method in patients with selective idiopathic hypopituitarism (particularly in those with growth-hormone deficiency) and in adults with autoimmune endocrine diseases. The results suggest that only when they are present at high titres may they be considered a good marker of pituitary involvement, and in particular of growth-hormone-producing cells.

Key words: lymphocytic hypophysitis; endocrine autoimmunity; anti-pituitary antibodies; immunofluorescence method.
Lymphocytic hypophysitis (LYH) is thought to represent an autoimmune disease of the pituitary gland which can impair pituitary hormonal secretion. Panhypopituitarism due to lymphoplasmacytic pituitary infiltration was described by Rapp and Pashkis in 1953, but they could not classify this disorder as autoimmune because the concept of endocrine autoimmunity was introduced some years later for Hashimoto’s thyroiditis. An autoimmune pathogenesis for LYH was suggested for the first time years later by Gaudie and Pinkerton, who described the occurrence of postpartum amenorrhoea and hypothyroidism in a young woman who subsequently died from severe acute secondary hyposurrenalism after appendicectomy. The autopsy revealed massive lymphoplasmacytic infiltration of both the pituitary and thyroid glands and adrenal atrophy. After this first description several case reports appeared in the literature, but these and the original series are generally of small size and have been accumulated over a number of years. Over the last 13 years the number of diagnosed cases has increased considerably, probably as a result of improved imaging criteria, and over 200 cases have been described so far. Nevertheless, at the present time the LYH is still considered uncommon, and its true incidence and prevalence are unknown.

CRITERIA FOR ORGAN-SPECIFIC AUTOIMMUNITY IN LYMPHOCYTIC HYPOPHYSITIS

For a long time, on the basis of the criteria for defining a disease as autoimmune, some endocrine diseases previously considered as idiopathic have been recognized as autoimmune. LYH fulfils most of the criteria required to define a disease as organ-specific autoimmune (Table 1).

Lymphocytic infiltration in the pituitary gland

In some endocrine diseases lymphocytic infiltration in the affected glands can be proven relatively easily due to the simple approach to the gland. This is certainly true in the case of autoimmune thyroid diseases but is much more difficult in many other autoimmune diseases, as in type 1 diabetes mellitus or Addison’s disease, whose autoimmune

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**Table 1. Criteria for organ-specific autoimmunity in lymphocytic hypophysitis (LYH).**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Presence in LYH</th>
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<tbody>
<tr>
<td>Lymphocytic infiltration of the target organ</td>
<td>Yes</td>
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<tr>
<td>Characteristic imaging suggestive of lymphocytic infiltration of the target organ</td>
<td>Yes</td>
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<tr>
<td>Presence of humoral or cellular autoimmune response in animals sensitized with autologous antigens</td>
<td>Yes</td>
</tr>
<tr>
<td>Organ-specific lesions in self-sensitized animals</td>
<td>Yes</td>
</tr>
<tr>
<td>Circulating autoantibodies against the target organ</td>
<td>Yes</td>
</tr>
<tr>
<td>Identification of the specific antigens</td>
<td>Discussed</td>
</tr>
<tr>
<td>Close association with other autoimmune diseases and or presence of other antibodies</td>
<td>Yes</td>
</tr>
<tr>
<td>Cycles of remission and relapses</td>
<td>Yes</td>
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<tr>
<td>Good response to immunosuppressive therapy</td>
<td>Yes</td>
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diagnosis can be achieved by searching for the respective organ-specific autoanti-
body. As regards LYH, histopathological observations, initially derived from autoptical or postsurgical pituitary examination, are more recently obtained by trans-sphenoidal pituitary biopsy, which until now was thought to be the diagnostic gold standard for LYH. The pathological findings are characterized by an inflammatory process with diffuse pituitary infiltration of lymphocytes, plasma cells and macrophagic cells. Lymphocyte aggregates, usually surrounding focal or diffuse areas of atrophic pituitary cells, are sometimes arranged in lymphoid follicles with a germinal centre. Unlike studies in the other autoimmune endocrine diseases, the expression of major histocompatibility complex (MHC) class II antigen on the pituitary cells from patients with LYH has not been identified.

**Morphological findings on MRI**

In some autoimmune endocrine diseases, such as chronic thyroiditis and central diabetes insipidus, a thyroid diffuse lymphocyte infiltration and a lymphocytic-infundibuloneurohypophysitis can be suggested by the presence of thyroid diffuse hypoechochogenic pattern on ultrasound and of pituitary stalk thickening on MRI, respectively.

As regards LYH, the presence of marked lymphocyte infiltration of the pituitary gland could be suggested by some particular morphological findings on MRI. In patients with LYH showing symptoms or signs related to pituitary enlargement, MRI evaluation is particularly important to differentiate LYH from adenoma in the sellar region, even if sometimes findings from imaging tend to overlap. On MRI, patients with LYH usually show a pituitary enlargement with symmetrical sovrasellar extension which can displace the optic chiasma, whereas patients with adenoma show asymmetrical pituitary enlargement with deviation of the stalk, which is instead thickened but usually not deviated in LYH. The pituitary enhancement after injection of gadolinium is homogeneously intense in LYH and shows a strip of enhanced tissue along the dura madre (also called ‘dural tail’). Patients with adenomas instead show delayed and poor enhancement, usually without a dural tail after gadolinium (Table 2).

**Animal models of lymphocytic hypophysitis**

Evidence of reproduction of the disease in experimental animals is considered another of the major criteria for defining a disease as autoimmune. Experimental subcutaneous injection of human anterior pituitary gland homogenates in Freund’s adjuvant into rats and rabbits produces a disease histopathologically similar to LYH. On the other hand, although the induction of LYH in hamsters is associated with the development of anti-pituitary antibodies, the passive transfer of these antibodies does not propagate

<table>
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<th>Table 2. Morphological findings suggestive of lymphocytic hypophysitis on MRI.</th>
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<tr>
<td>Pituitary enlargement with symmetrical sovrasellar expansion with possible compression and displacement of chiasma</td>
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<tr>
<td>Stalk thickened but not deviated</td>
</tr>
<tr>
<td>Intense and homogeneous enhancement of pituitary mass (after gadolinium)</td>
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<tr>
<td>Appearance of ‘dural tail’ (after gadolinium)</td>
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the disease. Recently, it has been shown in transgenic mice that the pituitary gland is susceptible to CD8 T-cell-mediated autoimmunity, triggered by viral infection (influenza virus); subsequently pan-anterior hypophysitis and dwarfism have been observed.

**Pituitary antigens and anti-pituitary antibodies**

Considerable progress has been made in understanding the autoimmune diseases over the last 20 years, particularly with regard to cloning of the antigens involved in the disease and the evolution of the laboratory assays for detection of organ-specific autoantibodies. Some autoantigens involved in LYH have been identified, and anti-pituitary antibodies (APAs) have been detected in patients with LYH, suggesting an autoimmune involvement in this disease (see below).

**Association with other autoimmune diseases and presence of other organ-specific antibodies**

The frequent association with other autoimmune diseases and the possible presence of other organ-specific autoantibodies in patients with LYH is a further argument supporting an autoimmune involvement in this disease. This is also backed up by the good response to immunosuppressive therapy and the occurrence of cycles of remission and relapse frequently observed during the natural history of the disease, by analogy with other autoimmune diseases. In fact, LYH is frequently associated with other endocrine and non-endocrine autoimmune diseases (Table 3). The most common association is with Hashimoto's thyroiditis or Graves' diseases. Moreover, an association with central diabetes insipidus, type 1 diabetes mellitus, Addison's disease, hypoparathyroidism, chronic atrophic gastritis, and pernicious anaemia has been described. Less frequently LYH can be associated with systemic lupus erythematosus, autoimmune hepatitis and primary biliary cirrhosis. Autoimmune diseases are characterized not only by their frequent association with other autoimmune diseases, but also by the presence of organ-/non-organ-specific autoantibodies with normal functional state or subclinical impairment of the respective glands. In patients with LYH

<table>
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<th>Table 3. Autoimmune diseases associated with lymphocytic hypophysitis.</th>
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<tr>
<td><strong>Relatively common</strong></td>
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<tr>
<td>Chronic autoimmune thyroiditis</td>
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<tr>
<td>Graves’ disease</td>
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<tr>
<td><strong>Relatively uncommon</strong></td>
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<tr>
<td>Central diabetes insipidus</td>
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<tr>
<td>Addison’s disease</td>
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<tr>
<td>Type 1 diabetes mellitus</td>
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<tr>
<td>Hypoparathyroidism</td>
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<tr>
<td>Chronic atrophic gastritis</td>
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<tr>
<td>Pernicious anaemia</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<tr>
<td>Primary biliary cirrhosis</td>
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some organ-specific antibodies can also be detected (Table 4). The coexistence in the same patient of two or more organ-specific and/or non-organ-specific autoimmune diseases indicates an autoimmune polyendocrine syndrome (APS). Taking into account this assumption, all patients with LYH associated with other autoimmune diseases can be considered as having an APS. In particular, when LYH is associated with hypoparathyroidism, mucocutaneous candidiasis and Addison’s disease, it could be included among the minor autoimmune diseases of APS type 1. Few cases of LYH could fall within the type 2 complete APS when it is associated with Addison’s disease, autoimmune thyroid diseases and/or type 1 diabetes mellitus. Moreover, LYH may be included in incomplete APS type 2, as in some of our cases with chronic autoimmune thyroiditis and presence of ACA, 21-OHAb and ICA. Most cases of LYH show characteristics of complete APS type 3 (autoimmune thyroid disease with or without other autoimmune diseases, but not Addison’s disease and hypoparathyroidism). Instead, when LYH does not fall within the above-mentioned combination, it can be included in type 4 APS (Figure 1). Concerning this, LYH may also be associated with autoimmune central diabetes insipidus.

### ANTI-PITUITARY ANTIBODIES

Organ-specific antibodies are good markers of many autoimmune endocrine diseases. Until now, APAs have not been considered good markers of LYH because of various difficulties in methodology and clinical interpretation. In fact, conflicting results in detecting APAs using different methods has impaired the clinical relevance of these antibodies. Moreover, a longitudinal study demonstrated that these antibodies can disappear over time; for this reason the time of detection could influence their identification.

### The complement consumption test

This was the first method used to detect APAs, testing plasma samples against human pituitary homogenate. Some women, tested in the first week after delivery, were positive for APAs and proceeded towards pituitary insufficiency. This method has not been used further by other researchers.

<table>
<thead>
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<th>Table 4. Organ-specific antibodies in lymphocytic hypophysitis.</th>
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<tr>
<td>Thyroperoxidase antibodies (TPOAbs)</td>
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<tr>
<td>Thyroglobulin antibodies (TgAbs)</td>
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<tr>
<td>Vasopressin-cell antibodies (AVPcAbs)</td>
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<tr>
<td>Islet-cell antibodies (ICAs)</td>
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<tr>
<td>Glutamic acid decarboxylase antibodies (GADAbs)</td>
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<tr>
<td>Adrenocortical antibodies (ACAs)</td>
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<tr>
<td>21-Hydroxylase antibodies (21-OHAbs)</td>
</tr>
<tr>
<td>Parietal-cell antibodies (PCAs)</td>
</tr>
<tr>
<td>Tissue transglutaminase antibodies (TTGAs)</td>
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Lymphocytic Hypophysitis

Addison’s disease and/or ACA, 21-OHAb
Chronic autoimmune thyroiditis and/or TPOAb, TgAb
Grave’s disease
Type 1 diabetes mellitus and/or ICA, GADAab

Figure 1. Lymphocytic hypophysitis in autoimmune polyendocrine syndromes (APSs).
The immunofluorescence method

The immunofluorescence method is one of the most widely used techniques for detecting APAs. An important issue that may contribute to the clarification of conflicting findings is the difference in the pituitary sections used in screening for APAs. Some studies have been performed on tissues from a variety of species and under a variety of conditions. A comparative study using porcine, rat, bovine, sheep, adult baboon, foetal cynomolgus and foetal human pituitary tissues showed that only human foetal pituitary should be used as substrate for APA evaluation in order to produce specific and reliable results. Other organ-specific antibodies are, in the majority of cases, only IgGs. Instead APAs include not only IgGs but also IgAs and more rarely IgMs; moreover, half of the IgGs are complement-fixing. Bottazzo et al characterized for the first time the hormone-secreting pituitary cells immunostained by APAs using a four-layer double-fluorochrome immunofluorescence. By analogy with other organ-specific autoantibodies (adrenocortical and steroid-cell antibodies, vasopressin-cell antibodies), APAs also react with cytoplasmic antigens (still unknown in this last case) distinct from pituitary hormones. These authors detected APAs at low titres in sera of some patients with APS or with isolated autoimmune endocrine diseases, providing evidence that APAs recognize exclusively PRL-secreting cells.

Moreover, none of the patients positive for PRL-cell antibodies showed an impairment of the pituitary function. Subsequently, APAs selectively staining growth hormone (GH) pituitary cells were demonstrated in a girl with Turner’s syndrome and partial GH deficiency (GHD) and in a patient with idiopathic GHD. APAs selectively immunostaining TSH-, LH-, FSH- and ACTH-secreting cells were detected in isolated cases of idiopathic TSH, LH, FSH and ACTH deficiency. A further problem with immunofluorescence was that APAs were demonstrated not only in some patients with biopsy-proven LYH or in patients with suspected LYH (patients with idiopathic hypopituitarism—isolated or associated with autoimmune endocrine diseases, patients with Sheehan’s syndrome or with empty sella syndrome) but also in patients with non-autoimmune pituitary diseases, such as ACTH-secreting adenoma or other pituitary adenomas.

The immunoblotting method

An alternative approach to APA detection was the immunoblotting method. This method utilized a homogenate of human autopsy pituitary tissue as substrate. The immunoblotting has been developed to identify the antigen target of APA. This method is capable of detecting multiple autoantigens at once; however, in spite of its quality, it is very difficult to standardize. Crock showed that serum antibodies against a 49 kDa pituitary cytosolic protein were present in 70% of patients with biopsy-proven LYH and in 55% of patients with suspected LYH, including patients with isolated ACTH deficiency, patients with hypopituitarism associated to other autoimmune diseases or females with Sheehan’s syndrome. However, APAs reactive to this protein were also found in many patients with other autoimmune endocrine diseases without LYH and in 20% of patients with hypopituitarism secondary to pituitary adenomas. Recently, the 49 kDa pituitary cytoplasmatic protein has been identified as an α-enolase, an enzyme ubiquitously expressed. Antibodies to α-enolase are not specific for LYH because they are frequently present in other autoimmune diseases. However, the authors
suggested that these antibodies may be helpful in the diagnosis of patients with LYH who would otherwise need pituitary biopsy.

The radioligand assay

Recently, APAs have been detected by radioligand assay. This method involves producing 35S-labelled pituitary-specific proteins by in vitro transcription/translation and then using these proteins in the immunoprecipitation assay. In particular Tanaka et al, using this method, demonstrated the presence of antibodies against GH and against pituitary-specific proteins called PGSF1 and PGSF2, respectively, in some patients with proven LYH and in some patients with idiopathic hypopituitarism, but not in patients with pituitary adenomas. Also antibodies to α-enolase were found by radioligand assay, confirming the results by immunoblotting assay in 41.2% of patients with LYH and in 23.5% of patients with idiopathic hypopituitarism. However, in contrast to the results obtained by immunoblotting, antibodies to α-enolase were found in 46% of patients with non-functioning adenomas, showing a similar frequency of these antibodies with respect to patients with LYH. Thus, the authors suggested that detection of α-enolase antibodies is not suitable for the specific diagnosis of LYH. The discrepancy between the results obtained by radioligand and immunoblotting assays in patients with pituitary adenoma may be explained by the different analytical methods. An important problem in these assays is that neither method is capable of showing what hormone-secreting cells APAs are immunostaining. Moreover, it seems impossible to show by immunoblotting some hypothetical antigens present in vivo because of their disappearance during the preparation.

Re-evaluation of APA detection by immunofluorescence

On the basis of these discrepancies between immunoblotting and radioligand methods, we recently performed a re-evaluation of APAs by indirect immunofluorescence using cryostat sections of young baboon pituitary glands (due to legal difficulties in obtaining human foetal pituitary tissue). APAs were evaluated in adults with idiopathic GHD, in adults with pituitary adenoma and in patients with autoimmune endocrine diseases. APAs were found at high titres in 33% of patients with idiopathic GHD but in no patients with acquired GHD. APAs were also detected at low titres in six of 20 patients (30%) with pituitary adenomas and in 40 of 180 patients (22.2%) with autoimmune endocrine diseases, 35 of them at low titres (87.5%) and five at high titres (12.5%). APA-positive patients at low titres had normal pituitary function, whereas all APA-positive patients at high titres had a severe isolated GHD. On the basis of these results, we suggested that a simple immunofluorescence method, using pituitary of young baboon as substrate, is a good approach for the detection of APAs. In particular, only when present at high titres may APAs be considered a good marker of pituitary involvement, not only in patients with apparently isolated idiopathic GHD but also in adults with autoimmune endocrine diseases with selective GHD. By subsequent retesting of the APA-positive sera of the previously studied patients, using a four-layer double-indirect immunofluorescence technique, we were able to demonstrate that the targets of APAs in patients with GHD are the somatrophs (De Bellis et al, unpublished data).
PATHOGENESIS

Autoimmune mechanisms characterizing other organ-specific autoimmune diseases are well known because of the ability to study animal models and the availability of target organ tissues from patients in the subclinical stage or at the clinical onset of the disease. At present, the mechanisms triggering the development and progression of LYH are not known, although the presence of animal models of LYH may open the way to understanding these events. 26–28 The role of CD8 T cells in autoimmune disease is gradually becoming better understood. In transgenic murine models it has been shown that CD8 T cells can mediate autoimmune encephalomyelitis, diabetes mellitus and, recently, LYH. 66–68 Indeed, endocrine organs, having a specialized vasculature into which large quantities of secreted proteins are released, may be particularly susceptible to autoimmune aggression with consequent endocrine deficiency. 29 In the pituitary of patients with LYH, mast cells are randomly distributed and also localized in the vicinity of capillaries. This could favour capillary permeability and angiogenesis, influencing the inflammatory and immunological aggression to pituitary cells. 69 As previously reported 29, de Jersey et al showed that transgenic murine pituitary gland is susceptible to CD8 T-cell-mediated pathology after infection with an influenza virus nucleoprotein, A/NT/60/68 (NP). In particular, on day 7 after infection, NP-specific T cells were detectable in the peripheral lymph nodes and spleen. However, 3–5 months after immunization, viral NP is expressed on the pituitary somatotrophs followed by migration to pituitary gland of NP-specific T cells. Despite the presence of activated IFN-γ-producing CD8 T cells in the pituitary gland, LYH is absent. When the frequency of specific T cells was artificially raised, LYH—characterized by severe GH deficiency and then multiple pituitary hormone deficiencies and dwarfism—occurred. 29,68 Major obstacles in understanding autoimmune pituitary mechanisms are the difficulties in obtaining pituitary tissue specimens with infiltrating lymphocytes and macrophagic cells from patients with LYH and a normal hypothalamic–pituitary region on MRI. However, histological studies of biopsy specimens of the pituitary glands from patients with LYH and an enlarged pituitary mass on MRI reveal inflammatory infiltrates occurring in the thyroid of patients with autoimmune chronic thyroiditis or Graves’ disease in active phases. In fact, these infiltrates are characterized above all by T lymphocytes (CD8 and CD4 cells) and B cells. 70 Moreover, it is possible that in LYH the damage resulting from infiltrating cytotoxic T cells could be the possible cause of the pituitary impairment, even if infiltrating B lymphocytes are able to produce specific APAs. As a consequence of lymphocytic infiltration, APAs become detectable in the sera and they could be considered markers of T-cell-mediated aggression to the pituitary gland in patients with silent LYH on MRI.

DIFFERENT EXPRESSIONS OF LYH DURING THE NATURAL HISTORY OF THE DISEASE

Some patients may present with symptoms and signs related to pituitary enlargement with possible extrasellar extension but without pituitary dysfunction, while others with normal characteristics on MRI may present with varying degrees of pituitary failure. 25,65,71 Moreover, many patients with LYH can show high levels of PRL, while others may have normal or even low levels of PRL (women with failure to lactate in the postpartum period). 1,6 The natural history of LYH is very variable, often showing during
its course an endless series of reversible changes in its morphological, clinical and immunological characteristics that contribute to misdiagnosis of the disease; as a result its prevalence is underestimated.\textsuperscript{9}

During the natural course of the disease spontaneous partial or total pituitary function recovery and/or mass resolution can occur.\textsuperscript{72} APAs, usually present at high titre initially, can subsequently disappear.\textsuperscript{73} Transient hypopituitarism can be explained by compression of pituitary cells by the inflammatory infiltrate and/or oedema.\textsuperscript{1,9} Instead, when cell destruction occurs, as observed in 10–15\% of cases, an evolution towards irreversible hypopituitarism can be observed.\textsuperscript{21} Finally, in some other cases the natural course of LYH is characterized by cycles of remissions and relapses. In this connection, since LYH most commonly occurs in women in late pregnancy or in the postpartum period, many patients with a previous diagnosis of Sheehan’s syndrome could actually be considered as having LYH.\textsuperscript{74}

**DIAGNOSIS OF LYH: ROLE OF ANTI-PITUITARY ANTIBODIES**

LYH has to be suspected in patients presenting with hyperprolactinaemia, headache, and impairment of visual field—especially if they are pregnant women or women with recent delivery and have symptoms of hypopituitarism of unclear aetiology. In these patients a trans-sphenoidal pituitary biopsy is thought to be the diagnostic gold standard for LYH.\textsuperscript{9} However, this procedure is invasive and not always feasible. Moreover, despite the recent development of sophisticated techniques of imaging, the diagnosis of LYH on MRI remains problematic because morphological findings of LYH on MRI can frequently overlap with those of pituitary adenoma.\textsuperscript{75} For this reason detection of APAs could be helpful for the diagnosis of LYH. In patients with pituitary enlargement the presence of APAs at high levels is suggestive for LYH; the presence at low titres or the absence of APAs can be suggestive of pituitary adenoma.\textsuperscript{41}

These autoantibodies can be used in diagnostic flow-charts in routine clinical practice to disclose some forms of LYH which are usually misdiagnosed. In particular, in patients with idiopathic selective hypopituitarism with normal hypothalamic–pituitary characteristics on MRI, detection of APAs is very suggestive for the diagnosis of LYH. As depicted in Figure 2, the presence of APAs at high titres in these patients allows unambiguous diagnosis of active LYH, whereas the detection of APAs at low levels could suggest the diagnosis of possible LYH of long duration. The absence of detectable APAs cannot exclude the possibility of an autoimmune origin for the disease, because autoantibodies could have been present in the past but may have disappeared by the time of the analysis.

Frequently, in patients with an autoimmune disease the presence of other autoantibodies but with normal function of the target gland could be possible.\textsuperscript{76–79} Betterle et al suggested that these patients could be considered as having a particular incomplete potential APS.\textsuperscript{15} For this reason, in patients with LYH, serological screening of other organ-specific or non-organ-specific antibodies could be performed (Figure 2). Moreover, APA screening in patients with organ-specific and non-organ-specific autoimmune diseases can be used for the discrimination of patients with an ongoing pituitary autoimmune process (Figure 3). Interestingly, the correct diagnosis of LYH depends in our experience on autoantibody titres. The presence of APAs at high titres allows the revelation of an LYH characterized by selective hypopituitarism with or
without pituitary enlargement on MRI. When APAs are present at low levels and pituitary function is normal, the presence of LYH could be excluded.

**THERAPEUTIC STRATEGIES**

Before the start of therapeutic strategies of LYH, two important considerations may be made: first, the different expressions of this autoimmune disease require different therapeutic strategies; and second, since a possible spontaneous remission during the natural history of LYH can be observed, the improvement occurring after surgical or medical treatment could be related to spontaneous resolution rather than to the treatment itself. For this reason a careful follow-up is advisable in patients without symptomatic extrasellar expansion or important hyposurrenalism. In fact, because most deaths in patients with LYH have been attributed to untreated adrenal insufficiency, glucocorticoid replacement using stress doses is essential in the acute setting. Surgical trans-sphenoidal treatment, with 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. In some cases pituitary biopsy is both diagnostic and therapeutic, because after this procedure a progressive recovery of pituitary function can be observed.
Glucocorticoids or other anti-inflammatory and immunosuppressive drugs (methotrexate, cyclosporin-A and azathioprine) have been suggested as medical treatment, but their long-term efficacy still needs to be confirmed. In some patients—in whom morphological pituitary characteristics of LYH on MRI overlap with findings of pituitary adenoma but APAs are present at high levels—high-dose methylprednisolone pulse therapy seems to be useful for both diagnostic and therapeutic procedures. In fact, in patients with LYH, but not in those with adenoma, pituitary mass reduction and a decrease in APAs could be observed after two cycles of this therapy.80

Therapy involves pituitary hormone replacement when LYH appears with hypopituitarism; because some or all pituitary deficiency may resolve, patients initially begun on treatment should be tested later to avoid unnecessary treatment.21 In fact, this resolution of the pituitary impairment after short-term pituitary hormone replacement can be attributed to a spontaneous resolution of the autoimmune process. However, pituitary hormone replacement could also act as an ‘isohormonal therapy’ in determining the restoration to the normal state of pituitary function in LYH. In particular, as demonstrated in other autoimmune diseases76,78,79 as well as in LYH, when the pituitary gland is not completely irreversibly destroyed, a feedback inhibition of pituitary gland function may decrease the exposure of putative pituitary autoantigens to further immune attack.

**Figure 3.** Diagnostic flowchart of LYH in patients with idiopathic selective hypopituitarism.
Practice points

- lymphocytic hypophysitis is thought a rare autoimmune disease but its true prevalence is probably underestimated
- an endless series of reversible changes in morphological, clinical and immunological characteristics shared with other diseases during the very variable natural history of lymphocytic hypophysitis could contribute to misdiagnosis of this disease
- a more accurate evaluation of the criteria required to define a disease as autoimmune could determine an increase in the incidence and prevalence of lymphocytic hypophysitis
- in patients showing symptoms or signs related to pituitary enlargement, histopathological characteristics are the gold standard for the diagnosis of lymphocytic hypophysitis
- lymphocytic hypophysitis is frequently associated with other autoimmune endocrine and non-endocrine diseases; the most common association is with Hashimoto's thyroiditis or Graves' disease
- many cases of lymphocytic hypophysitis could be included in complete type 3 autoimmune polyendocrine syndrome (autoimmune thyroid diseases without Addison disease)
- anti-pituitary antibodies have been detected in several patients with lymphocytic hypophysitis, but their role as a diagnostic marker needs to be clarified
- recently, a re-evaluation of APA detection has been performed in patients with lymphocytic hypophysitis
- APAs could be useful in clinical practice for diagnosis of particular forms of lymphocytic hypophysitis in which morphological characteristics on MRI are normal or inconclusive

Research agenda

- the pathogenesis of lymphocytic hypophysitis remains elusive at present, even though transgenic animal models suggest that CD8 T cells could mediate this disease
- mouse pituitary gland is susceptible to CD8 T-cell-mediated pathology after infection with an influenza virus nucleoprotein A-NT/60/68(NP)
- at the present time the role of anti-pituitary antibodies in lymphocytic hypophysitis is not clear because of conflicting results between different assay methods (immunofluorescence, immunoblotting, radioligand) for detecting these antibodies
- detection of anti-pituitary antibodies by immunofluorescence is problematic because studies have been performed on tissues from a variety of species and under a variety of conditions
- individual pituitary antigens have not been demonstrated by immunofluorescence
LYH fulfils most of the criteria required to define a condition as an organ-specific autoimmune disease. It has a special place among the spectrum of autoimmune diseases, particularly because of the different forms it takes during its natural history. The presence of clear morphological pituitary characteristics of LYH on MRI, followed by trans-sphenoidal pituitary biopsy, is the diagnostic gold standard for LYH in patients with hypopituitarism and symptoms and signs of an expanding pituitary mass. Despite the recent development of sophisticated diagnostic imaging, the diagnosis of LYH on MRI remains problematic. In particular, in these patients morphological findings of LYH on MRI can frequently overlap with findings of pituitary adenoma.

APAs have been detected in patients with LYH, suggesting an autoimmune involvement in this disease. Currently, APAs are still not considered good markers of LYH because of various difficulties in methodology and clinical interpretation. In fact, conflicting result in detecting APAs using different methods (immunofluorescence, immunoblotting, radioligand) has impaired the clinical relevance of these antibodies. Recently, detection of APAs by immunofluorescence has been re-evaluated, leading to the suggestion that they are legitimate organ-specific antibodies. In particular, APAs at high titres are useful for the diagnosis of LYH of recent onset in patients with apparently idiopathic selective hypopituitarism. Moreover, APAs screening has also been performed in patients with organ-specific autoimmune diseases for the discrimination of patients with an ongoing pituitary autoimmune process. It emerges that the detection of APAs is very helpful for a clear diagnosis of different forms of LYH.
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