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REVIEW

Immunological and clinical aspects of lymphocytic hypophysitis

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ABSTRACT

LYH (lymphocytic hypophysitis) is an autoimmune disease of the pituitary gland which can present with varying degrees of pituitary hormonal impairment and/or with symptoms related to pituitary enlargement. In this review, we provide an overview of the epidemiology, diagnosis, pathogenesis, treatment, and the role of organ-specific and antipituitary antibodies as potential markers of LYH. In addition, although the mechanisms underlying LYH are not completely understood, the role of prolactin, which plays an important part in maintaining immune system homoeostasis and is increased in the disease, is considered.

INTRODUCTION

LYH (lymphocytic hypophysitis) is an autoimmune disease of the pituitary gland [1], which can impair hormonal secretion from the pituitary. In 1953, Rapp and Pashkis [2] described a case of panhypopituitarism due to lymphoplasmacytic pituitary infiltration, but they were unable to classify this disorder as an autoimmune disease because the concept of endocrine autoimmunity had not been considered and was only introduced some years later for Hashimoto's thyroiditis [3]. Goudie and Pinkerton [4] described the occurrence of post-partum amenorrhoea and hypothyroidism in a young woman who subsequently died from severe acute secondary adrenal insufficiency after appendicectomy, suggesting the autoimmune involvement of the pituitary gland. After this first description, several case reports have appeared in the literature, but to date the number of LYH cases remain few [5,6] even though the number of cases diagnosed has increased, probably due to improved imaging criteria and techniques [7,8]. At present, LYH is still considered to be uncommon and its true prevalence is underestimated [9].

EPIDEMIOLOGY

LYH affects women more frequently than men, with a reported ratio of about 5:1 [10]. The mean age at diagnosis is approx. 35 years for women and 45 years for men. The disease appears to be influenced by geographic and ethnic factors. In the first series of patients, the Caucasian to Japanese ratio was approx. 3:1 [6] but, more recently, 130 out of 379 cases reviewed by Caturegli et al. [11] were Japanese. LYH appears to be strongly correlated with pregnancy as suggested by the frequent appearance from 6 months before to 6 months after delivery [6,10]; however, cases occurring outside pregnancy have been on the increase over the last few years [9,11]. The affected patients usually have a family or personal history of autoimmunity. The allele most frequently described in

Key words: antipituitary antibody, autoimmune disease, cytokine, immune system, lymphocytic hypophysitis (LYH), prolactin.
Abbreviations: APA, antipituitary antibodies; APS, autoimmune polyendocrine syndrome; DC, dentritic cell; GH, growth hormone; GHD, GH deficiency; IL, interleukin; IRF1, interferon regulatory factor 1; JAK, Janus kinase; LYH, lymphocytic hypophysitis; MRI, magnetic resonance imaging; PGSF, pituitary gland specific factor; PRL, prolactin; PRL-R, PRL receptor; STAT, signal transducer and activator of transcription; TDRD6, tudor-domain-containing protein 6.
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the few patients in whom studies have been performed is HLA DR4, although HLA DR5 has also been found [6].

MECHANISMS IN LYH

Inter-relationship between the neuroendocrine and immune systems

The neuroendocrine and immune systems are linked through a regulatory loop that allows a bi-directional communication between each other [12]. These interactions are mediated by hormones produced by the hypothalamus and pituitary gland acting on immune cells and by cytokines produced by the haemopoietic tissues, which exert regulatory influences on the hypothalamic–pituitary axis [13]. These interactions are necessary for the maintenance of homoeostasis during stress, infections and autoimmune diseases [14]. These conditions are known to evoke a neuroendocrine response termed the 'general adaptive syndrome', which is, in part, characterized by stimulation of HPA (hypothalamic–pituitary–adrenal) axis by cytokines produced at sites of inflammation. This results in an increased production of glucocorticoids [15,16], which can induce thymic involution, and decrease $CD4^+/CD8^+$ thymocytes and apoptosis with a possible interruption of autoimmune aggression. Stress also induces an increase in PRL (prolactin) and GH (growth hormone), which have been shown to counteract the effects of glucocorticoids [17]. In particular, *in vitro* studies have shown that PRL is able to prevent glucocorticoid-induced lymphocyte cell death (apoptosis), thus favouring the progression of an autoimmune process [18,19]. Thus PRL plays an important role in maintaining immune system homoeostasis [20]. Its role is amplified in LYH, in which the autoimmune process directly involves the pituitary gland, including PRL-secreting cells. High PRL levels have been frequently observed in patients with LYH accompanied by enlargement of the pituitary gland. Hyperprolactinaemia in such cases has been referred to as a decrease in the dopamine delivery to the anterior pituitary, due to stalk compression by pituitary suprasellary inflammatory mass or to direct escape of PRL into the circulation, secondary to massive cellular destruction [5,9,11].

The PRL/PRL-R (PRL receptor) unit and autoimmunity

In the human, mouse and rat genomes, a single gene found on chromosome 6 encodes PRL, mapping closely to MHC (on chromosome 6, 6p22.2-p21.3) in humans [21]. The PRL gene is 10 kb in size and is composed of five exons and four introns. It has been demonstrated that immune cells may produce PRL (via paracrine/autocrine secretion) [22], and the expression of the PRL gene (both mRNA and protein) has been observed in human T-cells, monocytes and B-cells [23]. Moreover, it has been suggested that PRL gene expression in lymphoid cells is regulated independently of the pituitary transcription factor Pit-1, due to the presence of a non-coding exon (exon1a); the immune cell transcript of the PRL gene is 150 nucleotides longer than its pituitary counterpart. The PRL peptide produced from this mRNA is, however, not different from that of pituitary origin [24].

Three principal forms of PRL (24, 21 and 11 kDa respectively) are synthesized and released from immune cells. Moreover, a portion of secreted PRL is phosphorylated; since phosphorylated PRL is reported to act as a partial agonist, the ratio between unphosphorylated and phosphorylated PRL may be physiologically relevant. As a result, PRL may not only be considered as an immunostimulatory endocrine factor, but also as an autocrine or paracrine immunoregulatory cytokine [25]. Furthermore, in human immune cells, PRL can be regulated by cytokines and other immune specific agonists [26].

The activities of PRL are mediated by the PRL-R, a member of cytokine receptor superfamily that includes receptors for GH, many cytokines and some growth factors [27,28]. The PRL-R gene is localized to chromosome 5p13 and is composed of 10 exons [29]. PRL-R is characterized by a single hydrophobic transmembrane domain, which divides the receptor into an extracellular-ligand-binding domain and an intracellular domain homologous with the GH receptor [30]. In particular, PRL-R is activated after dimerization, which occurs after ligand binding. Activated PRL-R stimulates the activation of JAK (Janus kinase), which leads to the tyrosine phosphorylation of PRL-R, followed by the thyrosine phosphorylation of latent STAT (signal transducer and activator of transcription) molecules [31]. In particular, STAT5 transactivation is required for transcription of several genes, including IRF1 (interferon regulatory factor 1) and SOCS (suppression of cytokine signalling) genes. Therefore pituitary PRL and immune-cell-derived PRL activate the JAK2/STAT pathway in immune cells to stimulate the expression of IRF1, which subsequently stimulates the transcription of IFNγ (interferon γ) [22]. PRL exerts a regulating effect on IRF1, an important immune factor in mediating antiviral and antibacterial responses, Th1 immune responses, macrophage and DC (dentritic cell) function, NK (natural killer) differentiation, cell-cycle progression and apoptosis. However, there is some evidence that PRL up-regulates not only Th1, but also Th2 cytokines [IL (interleukin)-4, IL-6 and IL-10].

It has been shown that the prevalent action of either Th1 or Th2 cells could determine not only the development of a particular autoimmune response, but also the progression (or not) towards a clinical stage of the disease. In particular, when PRL primarily stimulates DCs/Th1 cells, the activity of the corresponding autoimmune diseases may be exacerbated; instead, when

PRL stimulates predominantly Th2 cells, a possible activity towards remission of the autoimmune disease can occur through the shift from Th1 to Th2 cytokines [32]. Conversely, in Th2-mediated autoimmune diseases, PRL may increase the progression of the disease through its direct effects on Th2-related autoantibody production. Interestingly, an example of the role of PRL in shifting the balance between Th1 and Th2 cytokine responses is the behaviour of disease progression in some autoimmune diseases in pregnancy and in the post-partum period [33].

Pregnancy is characterized by a progressive rise in serum oestrogens, progesterone and PRL concentrations, as well as a number of placental hormones. Following delivery, oestrogen and progesterone secretion falls, whereas PRL secretion remains high, particularly in nursing females. Multiple changes in the immune system occur during pregnancy, which have been globally characterized as suppression of cell-mediated immunity and stimulation of humoral immunity [34]. These changes are consistent with DC/Th1-cell-mediated immunosuppressive effect of oestrogens and their stimulatory effect on Th2/B-cell function directly or through PRL stimulation. This could explain the high autoimmune susceptibility and the consequent higher prevalence of LYH in pregnancy and the post-partum period.

CLINICAL AND HORMONAL FINDINGS, AND NATURAL HYSTORY OF LYH

The symptoms and clinical signs of LYH (Table 1) are initially related to extrasellar pituitary enlargement due to oedema/infiltration of lymphocytes and plasma cells (early stage) [6]. In fact, during the natural history of the disease, some patients in the early stage may present with symptoms and clinical signs related to pituitary enlargement with possible extrasellar extension, including headache, visual field impairment, more rarely diplopia, with or without hypopituitarism. Hyperprolactinaemia is an usual finding in LYH, although more rarely PRL may be normal or even reduced [35].

Some patients in the early stage have normal characteristics by MRI (magnetic resonance imaging) despite presenting with various degrees of pituitary failure. Subsequently, during the natural course of the disease, spontaneous recovery of pituitary function with mass resolution can occur. This transient hypopituitarism can be due to a compression of pituitary cells by the inflammatory infiltrate or oedema. In some other cases, the natural course of LYH is characterized by cycles of remission and relapse. In this regard, as LYH occurs most commonly in women during late pregnancy or the post-partum period, many patients with a previous diagnosis of Sheehan's syndrome could actually be considered as having LYH [36].

Finally, when complete cell destruction occurs, the evolution towards irreversible hypopituitarism is usually observed [6]. In fact, basal and dynamic hormonal determination of the pituitary axis can show corticotropin ('ACTH') deficiency (most frequently isolated) [35], hypogonadotropic hypogonadism (usually diagnosed only in males), secondary hypothyroidism [11] and, more rarely, GHD [6]. In rare cases, adrenal insufficiency is acute and fatal [37,38]. These defects are considered as the direct result of an autoimmune attack on the pituitary cells. In addiction, when the process involves the infundibulum and the neurohypophysis, diabetes insipidus may be observed [10]. In some cases, LYH presentation is unusual. In particular, LYH can be associated with lachrymal, salivary and thyroid gland involvement [37], cystic appearance by MRI [38] or it can mimic a pituitary macroadenoma [39]. Frequently, LYH may be associated with other autoimmune diseases making up, in some cases, an APS (autoimmune polyendocrine syndrome) [9,40].

Table 1 Clinical and hormonal findings in LYH

LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Stage	Clinical manifestation	Hormonal finding
Early stage	Headache	Unusually normal pituitary function
	Visual field impairment	Hyperprolactinaemia
	Diplopia (more rarely)	Hypoprolactinaemia (more rarely)
		Subclinical hypopituitarism
Conclamate stage	Secondary adrenal insufficiency (rarely acute adrenal insufficiency)	Corticotropin deficiency
	Secondary hypothyroidism	TSH deficiency
	Hypogonadotropic hypogonadism	LH and FSH deficiency
	GHD syndrome in children and adults	Deficiency in GH

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES AND THE 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 [40]. This is also supported by a good response to immunosuppressive therapy, and the occurrence of cycles of remission and relapse frequently observed during the natural history of the disease, analogous with that described for other autoimmune diseases [41,42].

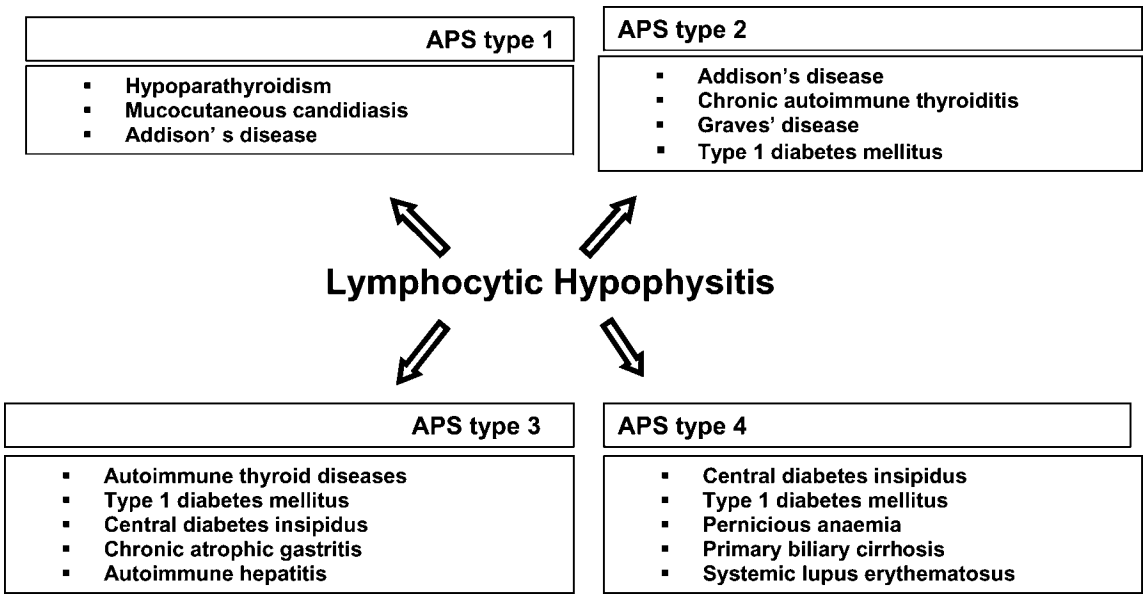

Figure 1 Association of LYH with other autoimmune diseases making up the different types of APS

In fact, LYH is frequently associated with other endocrine and non-endocrine autoimmune diseases. The most common association is with Hashimoto's thyroiditis or Graves' diseases [43]. Moreover, the association with central diabetes insipidus, Type 1 diabetes mellitus, Addison's disease, hypoparatiroidism, chronic atrophic gastritis and pernicious anaemia has been described [44–46]. Less frequently, LYH is associated with systemic lupus erythematosus and primary biliary cirrhosis [47,48]. Autoimmune diseases are also characterized by the presence of organ-/non-organ-specific autoantibodies with the normal functional state or subclinical impairment of the respective glands. In addition in patients with LYH, some organ-specific antibodies can be detected. The coexistence in the same patients of two or more organ-specific and/or non-organ-specific autoimmune diseases indicates 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 type 1 APS (Figure 1). A few cases of LYH fall within type 2 complete APS when it is associated with Addison's disease, autoimmune thyroid disease and/or Type 1 diabetes mellitus, whereas other cases of LYH are included in type 2 incomplete APS when associated with chronic autoimmune thyroiditis and presence of ACA (adrenocortical antibodies), 21-OHAb (21-hydroxylase antibody) and ICA (islet cell antibodies) [39]. Most cases of LYH have characteristics of type 3 complete APS (autoimmune thyroid disease with or without other autoimmune disease, but not Addison's disease or hypoparathyroidism). However, when LYH does not belong to any of the combinations mentioned above, it can be included in type 4 APS (Figure 1).

HISTOPATHOLOGY OF LYH

Histopathological findings in the first cases of LYH were usually derived from autopsy or post-surgical pituitary examination, whereas, in subsequent observations, specimens were obtained by trans-sfenoidal pituitary biopsy, which is still considered to be the gold standard diagnostic test for LYH [9,40]. The pathological findings are those of an inflammatory process with diffuse infiltration of lymphocytes and plasma cells. Lymphocytes are sometimes arranged in lymphoid follicles with a germinal centre, associated with focal or diffuse areas of atrophic pituitary cells surrounded by lymphoplasmacytic aggregates, whereas areas of reactive fibrosis can be observed in the remaining pituitary tissue. [9,11,40].

MORPHOLOGY OF LYH BY MRI

Although pituitary biopsy is still considered the gold standard diagnostic test for this disease, patients do not always consent to the procedure due to its invasive nature. The presence of marked lymphocyte infiltration of the pituitary gland in LYH could be also suggested by some particular morphological findings by MRI. In patients with LYH having symptoms or signs related to pituitary enlargement, MRI evaluation is particularly important to differentiate LYH from adenoma, even if findings from imaging sometimes tend to overlap. In fact, by MRI, patients with LYH usually have pituitary enlargement with a symmetrical suprasellar extension which can displace the optic chiasma, whereas patients with adenoma have asymmetrical pituitary enlargement with a deviation in the stalk, which is thickened but usually not deviated in LYH.

Pituitary enhancement after injection of gadolinium is homogeneously intense in LYH and has a strip of enhanced tissue along with dura mater, the so-called 'dural tail'. On the other hand, patients with adenoma have delayed and poor enhancement, usually without the 'dural tail' [49,50].

APA (ANTIPITUITARY ANTIBODIES)

Organ-specific antibodies are good markers of many autoimmune endocrine diseases [51–53] and, in LYH, APA are frequently present. However, to date, APA have not been considered good markers of LYH because of various difficulties in methodology and clinical interpretation. Several methods have been suggested for the detection of APA, but the most widely used are immunofluorescence and immunoblotting. In immunofluorescence methods, APA react with cytoplasmic antigens distinct from pituitary hormones, but the use of different pituitary substrates from humans or other animals may impair the interpretation of the results. Thus these antibodies have not been considered very specific and sensitive markers of autoimmune pituitary disease [54,55]. Using this method, Bottazzo et al. [56,57] have initially demonstrated that APA exclusively recognized PRL-secreting cells; however, none of the patients positive for PRL-cell antibodies had any impairment of pituitary function. Subsequently, APA to GH-secreting cells were first detected by Bottazzo et al. [57] in a girl with Turner's syndrome and partial GHD (GH deficiency), and in a patient with idiopathic GHD. A further problem with immunofluorescence was that APA were demonstrated not only in some patients with biopsy-proven LYH [58,59] or with suspected LYH, but also in patients with non-autoimmune pituitary diseases, such pituitary adenomas or empty sella syndrome [60]. The immunoblotting method utilizes a homogenate of human autopsy pituitary tissue as the substrate to identify the antigen target of APA. Using this method Crock [61] 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 corticotropin deficiency, patients with hypopituitarism associated with other autoimmune diseases or females with Sheehan's syndrome [61]. In particular, autoantibodies to a protein of 49 kDa have been observed in 21.5 % of patients with corticotopin deficiency, supporting the theory that autoimmune destruction of corticotrophs may be the cause of hormonal deficit in patients with corticotropin deficiency. This protein is a candidate marker for neuroendocrine autoimmunity [62]. Subsequently, these authors identified the 49 kDa pituitary cytoplasmatic protein as an α-enolase, an enzyme ubiquitously expressed and considered the antibodies to this antigen as markers of LYH [63]. However, subsequent studies suggested that antibodies to α-enolase cannot be considered specific for LYH because they are frequently present not only in patients with LYH, but also in some patients with hypopituitarism secondary to pituitary adenomas or to other pituitary diseases [64]. An alternative method is represented by radioligand assays which utilize ^{35}S-labelled pituitary-specific proteins, and this technique has been employed by some to detect antibodies against human GH and against two novel pituitary proteins, namely PGSF1 and PGSF2 (pituitary gland specific factor 1 and 2), in patients with LYH suspected on the basis of MRI [64]. Using this method, 18 % of patients with LYH and 9.7 % of patients with other autoimmune diseases, but not those with non-functioning adenoma, were positive for these antibodies, suggesting their usefulness in diagnosing LYH.

Recently, a new pituitary antigen has been identified in patients with GHD in type 1 APS. In particular, in some patients, antibodies against a TDRD6 (tudor-domain-containing protein 6) cDNA clone selectively immunostained 40–50 % of GH-secreting cells [65]. The authors suggested that TDRD6 is as a major autoantigen in patients with type 1 APS and that several sera from patients with GHD stain specific cells in the pituitary gland [65].

PATHOGENESIS

LYH is considered to be an autoimmune disorder as antibodies to the pituitary gland are detectable in serum and histopathological findings show that the gland is infiltrated by lymphocytes and plasma cells. Moreover, affected patients frequently have a personal or family history of other autoimmune disorders. In contrast with other autoimmune diseases, the mechanisms triggering the development and the progression of LYH are not well known, but the recent availability of animal models may open the way to a better understanding of the events leading to the pituitary damage. Similar to other conditions, CD8 T-cells are thought to mediate the autoimmune aggression of pituitary cells [66], as demonstrated in transgenic mice whose pituitaries were destroyed by CD8 T-cells after the injection of influenza virus nucleoprotein [67]. With regard to the role of APA, the disease cannot be reproduced by passive transfer of antibodies and, thus, these antibodies could be considered as markers of T-cell-mediated aggression to the pituitary cells, rather than pathogenic agents. In addition, the nature of the autoantigens involved in LYH is still unknown, although PGSF1a and PGSF2 [66], human GH, type 2 iodothyronine deiodinase [68] and neuron-specific enolase (α and γ isoforms) [63] have been suggested, but the list is growing.

ROLE OF APA IN LYH

The presence of clear morphological pituitary characteristics of LYH by MRI, followed by transphenoidal pituitary biopsy, are the gold standard diagnostic test for LYH in patients with hypopituitarism and symptoms and signs of an expanding pituitary mass. Despite the recent development of sophisticated diagnostic imaging techniques, the diagnosis of LYH by MRI remains problematic. In particular, in these patients, morphological findings of LYH by MRI can frequently overlap with those of pituitary adenoma. For this reason, detection of APA could be useful in the diagnosis of LYH. The presence of APA at high titres is suggestive of LYH, whereas, the absence or presence at low titres of APA is indicative of pituitary adenoma. The precise characterization of these antibodies may be obtained using a four-layer double fluorochrome immunofluorescence test in which antipituitary hormones/rabbit serum and rhodamine-conjugated anti-(rabbit IgG) are applied in the second sandwich assay [66].

Sauter et al. [69] detected APA selectively immunostaining cytoplasmatic granules in rat pituitary corticotrophs in a patient with idiopathic isolated corticotropin deficiency, but this protein has not been still characterized.

We characterized APA in adults and prepubertal children with idiopathic GHD [70–72], in children with coeliac disease with a lack of catch-up growth after a gluten-free diet [73] and, recently, in male adults with idiopathic hypogonadotropic hypogonadism [74]. APA against somatotrophs or gonadotrophs, when present at high titres, may be considered a good diagnostic marker of autoimmune forms of GHD and gonadotropin deficiency respectively. Moreover, we have shown that the detection of APA in children with idiopathic short stature could identify those prone to developing GHD in the future [71]. At present, it is not possible to establish whether APA are only good markers of an autoimmune pituitary process or if they also have a pathogenic role in LYH. However, in other autoimmune diseases, some organ-specific antibodies against key enzymes released by damaged cells are considered important diagnostic markers and are sometimes predictive of overt disease even without having a pathogenic role [51,52,75]. Screening of APA in patients with organ-specific and non-organ-specific autoimmune diseases can be used for discriminating patients with an ongoing pituitary autoimmune process [75,76]. Thus we suggest that, as well as for the organ-specific antibodies mentioned above, APA are good diagnostic and predictive markers of autoimmune pituitary impairment without a clear pathogenic role in LYH. These autoantibodies can be used in diagnostic flow charts in routine clinical practice for the discrimination of particular forms of LYH that are usually misdiagnosed.

THERAPEUTIC STRATEGIES

Two important considerations may be made. First, the different expressions of this autoimmune disease require different therapeutic strategies; secondly, a possible spontaneous remission during the natural history of LYH can be observed. For this reason, careful follow-up is advisable in patients without symptomatic extracellular expansion or important adrenal insufficiency [9,40].

In patients with symptoms and signs related to pituitary enlargement with a possible extrasellar extension, mass reduction can be achieved by pituitary surgery, dopamine agonists, anti-inflammatory/immunosuppressive drugs (glucocorticoids, methotrexate or azathioprine) or pituitary radiotherapy.

The role of neurosurgical therapy in the definitive treatment of LYH is controversial. This option should be chosen only in the presence of deficits in visual fields, visual acuity or ocular movements, because it can cause transitory or permanent complications such as bleeding, cerebrospinal fluid leaks and diabetes insipidus [11].

Glucocorticoids can be effective in the treatment of LYH to reduce the size of the pituitary mass and as a replacement therapy for adrenal function impairment. In some patients, in whom morphological pituitary characteristics of LYH by MRI overlap with findings of pituitary adenoma, high-dose methylprednisolone pulse therapy appears to be useful for both diagnostic and therapeutic procedures. In fact, in patients with LYH, pituitary mass reduction could be observed after two cycles of this therapy; however, the long-term efficacy still needs to be confirmed [9,11,40].

Pituitary stereotactic radiotherapy has been used successfully in two patients with LYH that were unresponsive to surgery or glucocorticoids [77], suggesting that this option may be a useful tool for patients with LYH resistant to conventional treatment, even if future studies in a larger cohort of patients will be needed to confirm this.

Dopamine agonists (bromocriptine or cabergoline) can lower hyperprolactinaemia and improve visual field alterations, but their impact on the course of LYH is still unproven [8,9].

Stable hypopituitarism in the course of LYH or due to neurosurgical therapy has to be corrected with appropriate replacement hormone therapy.

In other autoimmune diseases, 'isohormonal therapy' with the hormone of the affected gland can favour the recovery to a normal functional state when the gland is not completely and irreversibly destroyed [51–53,74]. Thus an early cycle of pituitary hormone replacement therapy could be also suggested as an 'isohormonal therapy' to determine the restoration of pituitary function in the subclinical phase of LYH; however, studies regarding this aspect are at present lacking in the literature.

CONCLUSIONS

LYH is a relatively rare disease, although the true prevalence is probably underestimated. It is considered to be an autoimmune disorder due to the detection of APA in serum from patients and histopathological findings showing that the gland is infiltrated by lymphocytes and plasma cells. Indeed, APA may have a potential role as diagnostic markers of the disease, but this remains to be clarified, and further studies are required to determine their use in clinical practice. The gold standard for the diagnosis of LYH in patients with symptoms or clinical signs related to pituitary enlargement is via biopsy and subsequent histopathology, although the combination of APA detection with MRI is increasingly being used and can be particularly important in differentiating LYH from adenoma.

LYH is also frequently associated with other autoimmune endocrine and non-endocrine diseases; the most common association is with Hashimoto's thyroiditis or Graves' disease. However, in contrast with other autoimmune diseases, the mechanisms triggering the development and progression of LYH are not well known, but the recent availability of animal models may shed light into the events leading to pituitary damage. A further understanding of the mechanisms and the potential role of PRL in this may provide useful information with regards to the treatment and management of patients with this disease.

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REFERENCES

1 Ezzat, S. and Josse, R. (1999) Autoimmune hypophysitis. In Autoimmune Endocrinopathies (Volpè, R., ed.), pp. 337–348, Humana Press, Totowa
2 Rapp, J. J. and Pashkis, K. E. (1953) Panhypopituitarism with idiopathic hypoparathyroidism. Ann. Intern. Med. **39**, 1103–1107
3 Roitt, I. M., Doniach, D., Campbell, P. N. and Hudson, R. V. (1956) Autoantibodies in Hashimoto's disease. Lancet **ii**, 820–822
4 Goudie, E. B. and Pinkerton, P. H. (1962) Anterior hypophysitis and Hashimoto's disease in a young woman. J. Pathol. Bacteriol. **83**, 584–585
5 Thodou, E., Asa, S. L., Kontogeorgos, G., Kovacs, K., Horvath, E. and Ezzat, S. (1995) Lymphocytic hypohysitis: clinicopathological findings. J. Clin. Endocrinol. Metab. **80**, 2302–2311
6 Beressi, N., Beressi, J. P., Cohen, R. and Modigliani, E. (1999) Lymphocytic hypophysitis: a review of 145 cases. Ann. Intern. Med. **150**, 327–341
7 Ahmadi, J., Scott Myers, G., Segall, H. D., Sharma, O. P. and Hinton, D. R. (1995) Lymphocytic adenohypophysitis: contrast-enhanced MR imaging in five cases. Radiology **195**, 30–34
8 Cheung, C. C., Ezzat, S., Smyth, H. S. and Asa, S. L. (2001) The spectrum and significance of primary hypophysitis. J. Clin. Endocrinol. Metab. **86**, 1048–1053
9 Bellastella, A., Bizzarro, A., Coronella, C., Bellastella, G., Sinisi, A. A. and De Bellis, A. (2003) Lymphocytic hypophysitis: a rare or underestimated disease? Eur. J. Endocrinol. **149**, 363–376
10 Hashimoto, K., Takao, T. and Makino, S. (1997) Lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis. Endocr. J. **44**, 1–10
11 Caturegli, P., Newschaffer, C., Olivi, A., Pomper, M. G., Burger, P. C. and Rose, N. R. (2005) Autoimmune hypophysitis. Endocr. Rev. **26**, 599–614
12 Besedovsky, H. O. and del Rey, A. (1996) Immune-neuro-endocrine interactions: facts and hypotheses. Endocr. Rev. **17**, 64–102
13 Chikanza, I. C. and Grossman, A. B. (2000) Reciprocal interactions between the neuroendocrine and immune systems during inflammation. Rheum. Dis. Clin. North Am. **26**, 693–711
14 Jara, L. J., Navarro, C., Medina, G., Vera-Lastra, O. and Blanco, F. (2006) Immune-neuroendocrine interactions and autoimmune diseases. Clin. Dev. Immunol. **13**, 109–123
15 Selye, H. (1998) A syndrome produced by diverse nocuous agents 1936. J. Neuropsychiatry Clin. Neurosci. **10**, 230–231
16 Nithya, K. and Buckley, A. R. (2004) Common signaling in the neuroendocrine and immune system. In Immunoendocrinology in Health and Disease (Geenen, V. and Chrousos, G., eds.), pp. 21–50, Marcel Dekker, New York
17 Chikanza, I. C. (1999) Prolactin and neuroimmunomodulation: *in vitro* and *in vivo* observations. Ann. N.Y. Acad. Sci. **22**, 119–130
18 La Voie, H. A. and Witorsch, R. J. (1995) Investigation of intracellular signals mediating the anti-apoptotic action of prolactin in Nb2 lymphoma cells. Proc. Soc. Exp. Biol. Med. **209**, 257–269
19 Buckley, A. R. (2001) Prolactin, a lymphocyte growth and survival factor. Lupus **10**, 684–690
20 Richards, S. M. and Murphy, W. J. (2000) Use of human prolactin as a therapeutic protein to potentiate immunohematopoietic function. J. Neuroimmunol. **109**, 56–62
21 Matera, L. and Rapaport, R. (2002) NeuroImmune Biology, vol. 2: Growth and Lactogenic Hormones, Elsevier, Amsterdam
22 Hooghe, R., Martens, N. and Hooghe-Peters, E. L. (2004) Prolactin and the immune system. In Immunoendocrinology in Health and Disease (Geenen, V. and Chrousos, G., eds.), pp. 207–239, Marcel Dekker, New York
23 Pellegrini, I., Lebrun, J. J., Ali, S. and Kelly, P. A. (1992) Expression of prolactin and its receptor in human lymphoid cells. Mol. Endocrinol. **6**, 1023–1031
24 Gellersen, B., Kempf, R., Telgmann, R. and Di Mattia, G. E. (1994) Nonpituitary human prolactin gene transcription is independent of Pit-1 and differentially controlled in lymphocytes and in endometrial stroma. Mol. Endocrinol. **8**, 356–373
25 Gutierrez, M. A., Molina, J. F., Jara, L. J. et al. (1995) Prolactin and systemic lupus erythematosus: prolactin secretion by SLE lymphocytes and proliferative (autocrine) activity. Lupus **4**, 348–352
26 Gerlo, S., Verdood, P., Hooghe-Peters, E. L. and Kooijman, R. (2005) Modulation of prolactin expression in human T lymphocytes by cytokines. J. Neuroimmunol. **162**, 190–193
27 Matera, L. (1997) Action of pituitary and lymphocyte prolactin. NeuroImmunoModulation **4**, 171–180
28 Bazan, J. F. (1989) A novel family of growth factor receptors: a common binding domain in the growth hormone, prolactin, erythropoietin and IL-6 receptors, and the p75 IL-2 receptor β-chain. Biochem. Biophys. Res. Commun. **31**, 788–795
29 Gearing, D. P., Druck, T., Huebner, K. et al. (1993) The leukemia inhibitory factor receptor (LIFR) gene is located within a cluster of cytokine receptor loci on mouse chromosome 15 and human chromosome 5p12-p13. Genomics **18**, 148–150
30 Horseman, N. D. (2002) Prolactin receptor diversity in humans: novel isoforms suggest general principles. Trends Endocrinol. Metab. **13**, 47–48

31 Dorshkind, K. and Horseman, N. D. (2000) The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency. Endocr. Rev. **21**, 292–312
32 McMurray, R. W. (2001) Estrogen, prolactin, and autoimmunity: actions and interactions. Int. Immunopharmacol. **1**, 995–1008
33 McMurray, R. W. (2001) Bromocriptine in rheumatic and autoimmune diseases. Semin. Arthritis Rheum. **31**, 21–32
34 Formby, B. (1995) Immunologic response in pregnancy. Its role in endocrine disorders of pregnancy and influence on the course of maternal autoimmune diseases. Endocrinol. Metab. Clin. North Am. **24**, 187–205
35 Abe, T., Matsumoto, K., Sanno, N. and Osamura, Y. (1995) Lymphocytic hypophysitis: case report. Neurosurgery **36**, 1016–1019
36 Goswami, R., Kochupillai, N., Crock, P. A., Jaleel, A. and Gupta, N. (2002) Pituitary autoimmunity in patients with Sheehan's syndrome. J. Clin. Endocrinol. Metab. **87**, 4137–4141
37 Asa, S. L., Bilbao, J. M., Kovacs, K., Josse, R. G. and Kreines, K. (1981) Lymphocytic hypophysitis of pregnancy resulting in hypopituitarism: a distinct clinicopathologic entity. Ann. Intern. Med. **95**, 166–171
38 Blisard, K. S., Pfalzgraf, R. R. and Balko, M. G. (1992) Sudden death due to lymphoplasmacytic hypophysitis. Am. J. Forensic Med. Pathol. **13**, 207–210
39 Yamaguchi, S., Kato, T., Takeda, M., Anzai, J. and Ikeda, H. (2005) A case of lymphocytic hypophysitis mimicking pituitary macroadenoma. No Shinkei Geka **33**, 971–977
40 De Bellis, A., Bizzarro, A. and Bellastella, A. (2005) Pituitary antibodies and lymphocytic hypophysitis. Best Pract. Res. Clin. Endocrinol. Metab. **19**, 67–84
41 Matta, M. P., Kany, M., Delisle, M. B., Lagarrigue, J. and Caron, P. H. (2002) A relapsing remitting lymphocytic hypophysitis. Pituitary **5**, 37–44
42 Yamagami, K., Yoshioka, K., Sakai, H. et al. (2003) Treatment of lymphocytic hypophysitis by high-dose methylprednisolone pulse therapy. Intern. Med. **42**, 168–173
43 Barbaro, D. and Loni, G. (2000) Lymphocytic hypophysitis and autoimmune thyroid disease. J. Endocrinol. Invest. **23**, 339–340
44 Vandewalle, C. L., Falorni, A., Svanholm, S., Lernmark, A., Pipeleers, D. G. and Gorus, F. K. (1995) High diagnostic sensitivity of glutamate decarboxylase autoantibodies in insulin-dependent diabetes mellitus with clinical onset between age 20 and 40 years. The Belgian Diabetes Registry. J. Clin. Endocrinol. Metab. **80**, 846–851
45 Betterle, C., Greggio, N. A. and Volpato, M. (1998) Autoimmune polyglandular syndrome type 1. J. Clin. Endocrinol. Metab. **83**, 1049–1055
46 Precotto, F., Pedini, B. and Betterle, C. (1997) Autoimmunità nelle malattie dell'ipofisi e della pineale. In Gli Autoanticorpi (Betterle, C., ed.), pp. 195–201, Piccin, Padova
47 Ji, J. D., Lee, S. Y., Choi, S. J., Lee, Y. H. and Song, G. G. (2000) Lymphocytic hypophysitis in a patient with systemic lupus erythematosus. Clin. Exp. Rheumatol. **8**, 78–80
48 Pinol, V., Cubiella, J., Navata, M. et al. (2000) Autoimmune hepatitis associated with thyroiditis and hypophysitis. A case report. J. Gastroenterol. Hepatol. **23**, 123–125
49 Levine, S. N., Benzel, E. C., Fowler, M. R., Shroyer, III, J. V. and Mirfakhraee, M. (1988) Lymphocytic adenohypophysitis: clinical, radiological, and magnetic resonance imaging characterization. Neurosurgery **22**, 937–941
50 Sato, N., Sze, G. and Endo, K. (1998) Hypophysitis: endocrinologic and dynamic MR findings. AJNR, Am. J. Neuroradiol. **19**, 439–444
51 De Bellis, A., Bizzarro, A., Rossi, R., Amoresano Paglionico, V., Criscuolo, T., Lombardi, G. and Bellastella, A. (1993) Remission of subclinical adrenocortical failure in subjects with adrenal autoantibodies. J. Clin. Endocrinol. Metab. **76**, 1002–1007
52 De Bellis, A., Colao, A., Di Salle, F. et al. (1999) A longitudinal study of vasopressin cell antibodies, posterior pituitary function, and magnetic resonance imaging evaluations in subclinical autoimmune central diabetes insipidus. J. Clin. Endocrinol. Metab. **84**, 3047–3051
53 De Bellis, A., Bizzarro, A., Amoresano Paglionico, V. et al. (1994) Detection of vasopressin cell antibodies in some patients with autoimmune endocrine disease without overt diabetes insipidus. Clin. Endocrinol. **40**, 173–177
54 Gluck, M. and Scherbaum, W. A. (1990) Substrate specificity for the detection of autoantibodies to anterior pituitary cells in human sera. Horm. Metab. Res. **22**, 541–545
55 Maghnie, M., Lorini, R. and Severi, F. (1994) Antipituitary antibodies in patients with pituitary abnormalities and hormonal deficiency. Clin. Endocrinol. **40**, 809–810
56 Bottazzo, G. F., Pouplard, A., Florin-Christensen, A. and Doniach, D. (1975) Autoantibodies to prolactin-secreting cells of human pituitary. Lancet **ii**, 97–101
57 Bottazzo, G. F., McIntosh, C., Stanford, W. and Preece, M. (1980) Growth hormone cell antibodies and partial growth hormone deficiency in a girl with Turner's syndrome. Clin. Endocrinol. **12**, 1–9
58 Pouplard, A. (1982) Pituitary autoimmunity. Horm. Res. **16**, 289–297
59 Mayfield, R. K., Levine, J. H., Gordon, L., Powers, J., Galbraith, R. M. and Rawe, S. E. (1980) Lymphoid adenohypophysitis presenting as a pituitary tumor. Am. J. Med. **69**, 619–623
60 Scherbaum, W. A., Schrell, U., Gluck, M., Fahlbusch, R. and Pfeiffer, E. F. (1987) Autoantibodies to pituitary corticotropin-producing cells: possible marker for unfavourable outcome after pituitary microsurgery for Cushing's disease. Lancet **i**, 1394–1398
61 Crock, P. (1998) Cytosolic autoantigens in lymphocytic hypophysitis. J. Clin. Endocrinol. Metab. **83**, 609–618
62 Bensing, S., Kasperlik-Zaluska, A. A., Czarnocka, B., Crock, P. A. and Hulting, A. (2005) Autoantibodies against pituitary proteins in patients with adrenocorticotropin-deficiency. Eur. J. Clin. Invest. **35**, 126–132
63 O'Dwyer, D. T., Smith, A. I., Matthew, M. L. et al. (2002) Identification of the 49-kDa auoantigen associated with lymphocytic hypophysitis as a-enolase. J. Clin. Endocrinol. Metab. **87**, 752–757
64 Tanaka, S., Tatsumi, K. I., Takano, T. et al. (2003) Anti-alpha-enolase antibodies in pituitary disease. Endocr. J. **50**, 697–702
65 Bensing, S., Fetissov, S. O., Mulder, J. et al. (2007) Pituitary autoantibodies in autoimmune polyendocrine syndrome type 1. Proc. Natl. Acad. Sci. U.S.A. **104**, 949–954
66 Sun, D., Whitaker, J. N. and Huang, Z. (2001) Myelin antigen-specific CD8+ T cells are encephalitogenic and produce severe disease in C57BL/6 mice. J. Immunol. **166**, 7579–7587
67 De Jersey, J., Carmignac, D. and Le Tissier, P. (2004) Factors affecting the susceptibility of the mouse pituitary gland to CD8 T-cell-mediated autoimmunity. Immunology **111**, 254–261
68 Nakahara, R., Tsunekawa, K., Yabe, S. et al. (2005) Association of pituitary antibody and type 2 iodothyronine deiodinase antibody in patients with autoimmune thyroid disease. Endocr. J. **52**, 691–699
69 Sauter, N. P., Toni, R., McLaughlin, C. D., Dyess, E. M., Kritzman, J. and Leuchan, R. M. (1990) Isolated adrenocorticotropin deficiency associated with an autoantibody to a corticotroph antigen that is not adrenocorticotropin or other propriomelanocortin-derived peptides. J. Clin. Endocrinol. Metab. **70**, 1391–1397
70 De Bellis, A., Bizzarro, A., Perrino, S. et al. (2005) Characterization of antipituitary antibodies targeting pituitary hormone-secreting cells in idiopathic growth hormone deficiency and autoimmune endocrine disease. Clin. Endocrinol. **63**, 45–49
71 De Bellis, A., Bizzarro, A., Conte, M. et al. (2003) Antipituitary antibodies in adults with apparently idiopathic growth hormone deficiency and in adults with autoimmune endocrine diseases. J. Clin. Endocrinol. Metab. **88**, 650–654

72 De Bellis, A., Salerno, M., Conte, M. et al. (2006) Antipituitary antibodies recognized GH-producing cells in children with idiopathic growth hormone deficiency and in children with idiopathic short stature. J. Clin. Endocrinol. Metab. **91**, 2484–2489
73 Iughetti, L., De Bellis, A., Predieri, B. et al. (2006) Growth hormone impaired secretion and antipituitary antibodies in patients with coeliac disease and poor catch-up growth after a long gluten-free diet period: a causal association? Eur. J. Pediatr. **165**, 897–903
74 De Bellis, A., Sinisi, A. A., Conte, M. et al. (2007) Antipituitary antibodies against gonadotropin-secreting cells in adult male patients with apparently idiopathic hypogonadotropic hypogonadism. J. Clin. Endocrinol. Metab. **92**, 604–607
75 De Bellis, A., Falorni, A., Laureti, S. et al. (2001) Time course of 21-hydroxylase antibodies and long-term remission of subclinical autoimmune adrenalitis after corticosteroid therapy: case report. J. Clin. Endocrinol. Metab. **86**, 675–678
76 Manetti, L., Lupi, I., Morselli, L. L. et al. (2007) Prevalence and functional significance of antipituitary antibodies in patients with autoimmune and non-autoimmune thyroid diseases. J. Clin. Endocrinol. Metab. **96**, 2176–2181
77 Selch, M. T., DeSalles, A. A., Kelly, D. F. et al. (2003) Stereotactic radiotherapy for the treatment of lymphocytic hypophysitis. Report of two cases. J. Neurosurg. **99**, 591–596

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