

Lymphocytic hypophysitis: Disease spectrum and approach to diagnosis and therapy

Juan-Andres Rivera

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Abstract Lymphocytic hypophysitis (LYH) is a neuroendocrine disorder characterized by autoimmune inflammation of the pituitary gland with various degrees of pituitary dysfunction. The histopathology consists of an initial monoclonal lymphocytic infiltrate, which can heal with minimal sequela or progress to fibrosis and result in permanent hypopituitarism. Coexistence of other autoimmune conditions is reported in 25–50% of cases and pituitary autoantibodies have been detected in up to 70% of biopsy-proven cases. The clinical presentation varies depending on the pituitary segment that is more severely affected. In lymphocytic *adenohypophysitis* (LAH) an early destruction of the ACTH-producing cells is characteristic. Other anterior pituitary hormones can also be affected but posterior pituitary involvement is absent or minimum. Lymphocytic *Infundibuloneurohypophysitis* (LINH) typically presents as acute onset diabetes insipidus (DI) with intracranial mass-effect symptoms. A combination of extensive anterior pituitary involvement and DI characterizes lymphocytic *Infundibulopanhypophysitis* (LIPH). The diagnosis can be challenging in many cases, because distinction from pituitary adenomas and other sellar masses is not obvious. Significant efforts have been made to identify specific serum markers, but it would seem unlikely that this approach will ever have the specificity to replace histopathological examination of a surgical specimen. Diagnostic criteria have

been proposed to help in the decision-making process and to avoid, whenever possible, unnecessary invasive procedures. The therapeutic approach is controversial and, although transsphenoidal surgery is often performed, a conservative medical management is justified in many cases, given the self-limited nature of the inflammatory process. This paper reviews the etiology, epidemiology, clinical and radiological findings, diagnosis and management of LYH.

Keywords Lymphocytic hypophysitis · Autoimmune hypophysitis · Pituitary inflammation · Hypopituitarism

Introduction

The pituitary gland is occasionally the target of inflammatory response to local infections, neoplasias or autoimmune reactions. Lymphocytic hypophysitis (LYH) is the term commonly used to refer to such processes when an autoimmune origin is considered. This condition is characterized by lymphocytic infiltration and eventually destruction of the pituitary tissue accompanied by various degrees of pituitary dysfunction. As with other autoimmune conditions, LYH is seen more frequently in women [1]; in fact, it was initially considered to be restricted to women in relationship with pregnancy [2]. With an increasing number of cases in children, postmenopausal women and men reported in recent years, it is now clear that LYH can occur in children and adults, males and females [3–10].

In classical LYH, inflammation is limited to the anterior pituitary or adenohypophysis; therefore, it is often referred to in the literature as lymphocytic *adenohypophysitis* (LAH) [11]. In contrast, when diabetes insipidus (DI) is prominent, either as the presenting or dominant symptom,

J.-A. Rivera
Division of Endocrinology, McGill University and McGill
University Health Centre,
Montreal, Quebec, H3A 1A1, Canada

J.-A. Rivera (✉)
687 Pine Av West, Room M9.54 Royal Victoria Hospital,
Montreal, Quebec, H3A 1A1, Canada

or as a permanent sequela, the term lymphocytic *infundibuloneurohypophysitis* (LINH) is preferred [12]. Pathologic examination of tissue from patients with LINH has in fact revealed lymphocytic inflammation limited to the infundibulum, the pituitary stalk and the neurohypophysis [13]. Cases of LINH have been reported with increasing frequency in the last decade [14–26] and this condition is now regarded as a LYH variant. LINH is also referred to as stalkitis, infundibulo-stalkitis, neurohypophysitis and necrotizing infundibulo-hypophysitis [14,22]. Interestingly, LINH seems to occur more often in young men and in children.

This review discusses the etiology, clinical presentation, diagnostic and therapeutic aspects of LYH in all its variants.

Historical background

Although the first reported case of Lymphocytic Hypophysitis is generally credited to Goudie and Pinkerton in 1962 [2], a paper by Rapp and Rashkis published years before, in 1953, had already described the typical pathology findings in the pituitary gland in association with panhypopituitarism [27]. Nevertheless, the report by Goudie and Pinkerton has the merit of highlighting the classical clinical features of this condition and postulating an autoimmune etiopathogenic mechanism. They described a 22-year-old woman who developed postpartum hypothyroidism and amenorrhea. Hypoadrenalism was evident only fourteen months after childbirth, when during an appendectomy she developed shock and died. An autopsy revealed lymphocytic thyroiditis, severely atrophic adrenals and a small atrophic pituitary with extensive lymphocytic infiltration. No giant cells or granulomas were seen and pathology was distinct enough to differentiate it from healed postpartum pituitary necrosis (Scheehan's syndrome) and granulomatous hypophysitis.

In 1970 Saito et al. [28] and, 20 years later, Kojima et al. [29] made the first pathological descriptions of LINH. They reported postmortem findings in elderly patients with central DI (CDI). In these cases lymphocytic infiltration was limited to the infundibulum, the stalk and the neurohypophysis [11].

After these initial reports, LYH has been recognized and reported with increasing frequency by clinicians and pathologists, and is now accepted as a distinct clinical entity of variable presentation.

Etiopathology

An autoimmune etiology of LYH is supported by several facts: first, its frequent association with other autoimmune conditions; second, its increased incidence in women and in relation with pregnancy; third, the pathologic appearance of the affected pituitary tissue in autopsy and biopsy specimens;

and finally, the presence of pituitary autoantibodies in serum from affected patients.

Associated autoimmune conditions

Concurrent autoimmune conditions are reported in 20–50% of cases of LYH [1,11,12,30–33]. The onset of these conditions can precede, or follow the onset LYH. Most common association is with autoimmune thyroid disease, reported in 15–25% of LYH cases, i.e. 70–80% of cases with an associated autoimmune disease [1,2,11,31,33]. Of these, about 75% are chronic autoimmune thyroiditis (Hashimoto's thyroiditis); while Graves disease and sub-acute thyroiditis are reported less frequently [11,34]. Autoimmune adrenalitis is reported in 5–7% of cases [15–25% of patients with an associated autoimmune condition); while pernicious anemia and type 1 diabetes mellitus are seen in 2% of cases [11,12]. Association with other autoimmune conditions such as vitiligo [1,3], focal lymphocytic parathyroiditis [11,32], polyglandular autoimmune syndrome type 2, celiac disease, systemic lupus erithematosus and rheumatoid arthritis [7,8,12,35], has also been reported.

Single case reports have described LINH in association with two other conditions: Adults Still's disease [36], a rare inflammatory process of unknown etiology, and recurrent optic neuritis [37]. In both these processes autoantibodies are possibly involved.

Pituitary autoantibodies

Levine produced in 1967 an animal model of autoimmune hypophysitis. He induced what he called an "allergic adeno-hypophysitis" by injecting rats with a mixture of autologous pituitary tissue and Freund's adjuvant [2]. In similar experiments Watanabe et al. [38] identified antibodies to growth hormone (GH), thyrotropin (TSH), and luteinizing hormone (LH) as the main antibodies involved. Another animal model for the disease was generated by Yoon et al. [39]. They injected hamsters with rubella virus membrane-associated E1 and E2 glycoproteins, thus consistently inducing autoimmune lymphocytic hypophysitis evidenced by serum autoantibodies against pituitary cells and lymphocytic infiltration of the pituitary, all of which was prevented by neonatal thymectomy. This suggests two things: first, that viral antigens may be involved in triggering the autoimmune process; and second, that a cellular immune response is required. Some groups have detected anti-GH and anti-prolactin antibodies in serum from patients with LYH [40,41]. Takao et al. [41] identified autoantibodies against GH with significantly high frequency in sera from patients with both LYH (11 of 15, 73.3%) and isolated ACTH deficiency (7 of 9, 77.8%).

In 1998, Crock [30] reported the detection, by immunoblotting, of autoantibodies to a 49-kDa cytosolic pituitary protein in the serum of patients with LYH, with titers as high as 1:1000 in 7 out of 10 patients with biopsy-proven, and in 11 of 22 with suspected LYH. This antibody was also detected in a smaller percentage of patients with other autoimmune or pituitary disorders, including Addison's disease (42%), pituitary tumors (20%), thyroid autoimmunity (15%) and rheumatoid arthritis (13%). This antigen appears to be the ubiquitous glycolytic enzyme, alpha-enolase [42]. Additional research has shown that autoantibodies detected in the serum of patients with LYH react as well against another isoform of this enzyme, gamma-enolase, better known as neuron-specific enolase (NSE), which is restricted to neuronal tissue and neuroendocrine cells [43]. Since NSE is also expressed in placental tissue, it is viewed as a potential rationale for the association of LYH with pregnancy. Although its expression in normal pituitary tissue appears to be very heterogeneous, all pituitary cell subtypes seem to express NSE [44]. However, many studies looking at the expression of NSE in pituitary cells have often used antibodies that could cross-react with other enolase isoforms. Therefore, further research may be necessary to detect specific enolase isoforms that may be expressed differentially in pituitary cells subtypes and, hence, explain the particularly high susceptibility of the corticotroph and to a lesser extent the thyrotroph, in LAH. A number of other anti-pituitary autoantibodies have been detected in patients with LYH and in other seemingly unrelated conditions such as diabetes mellitus type 2 (for review see 27). Because of their lack of specificity, some neuroendocrinologists consider these autoantibodies an epiphenomenon rather than a causal of the disease [33], which is in contradiction with an autoimmune etiology in LYH. We believe that, as disappointingly non-specific as they may seem to be at present, antipituitary antibodies are most likely at the core of the mechanism of disease in LYH.

In a case of LINH, Hashimoto et al. [12] found antibodies to an unidentified 29-kDa antigen of the human anterior pituitary cytosol. In cases of idiopathic CDI, Scherbaum et al. [45] found autoantibodies to vasopressin (AVP)-secreting hypothalamic cells (AVPcAb) in 31%. Fifty-four percent of patients with CDI secondary to histiocytosis X were also positive. In a more recent report De Bellis et al. [46] show that 15 of 22 (68%) patients with CDI and autoimmune polyendocrine syndrome (APS) had AVPcAb. When classified according to the duration of the CDI, 8 of 10 (80%) with CDI for less than 18 months were AVPcAb positive, compared with 7 of 12 (58.3%) of those with CDI for 7 years or more. In addition, they found a positive correlation between pituitary stalk thickening and titers of AVPcAb in patients with CDI of recent onset. Therefore, in many cases, isolated

CDI may represent a form LINH that has passed otherwise unnoticed.

Since these data suggests that different antigens may be involved in different clinical variants of LYH, it would appear that, while these conditions share similar etiology and mechanisms of disease, they represent distinct clinical entities. Given the lack specificity encountered so far, further research would be necessary to elucidate a reproducible and cost-effective antibody screening approach in suspected cases. Clearly it is unlikely that this approach will ever have the specificity to replace histopathological examination of a pituitary biopsy.

Histopathology

Histopathology remains the gold standard for diagnosis of LYH. A diffuse polyclonal lymphocytic infiltration with predominance of T cells, particularly CD4 cells is characteristic [13,15,17,47]. Scattered plasma cells, a few eosinophils, edema, and fibrosis replacing pituitary acini are also commonly present [1,31]. Electron microscopy has shown interdigitation of inflammatory cells with pituicytes [32] and the presence of lysosomal bodies and oncocyctic changes in some pituitary cells [1]. The absence of multinucleated giant cells, epithelioid histiocytes and true granulomas distinguishes LYH from granulomatous hypophysitis, which tends to occur in older patients and in relation with systemic granulomatous diseases (sarcoidosis, tuberculosis, histiocytosis). Fibrosis is also seen in Sheehan's syndrome but there the pattern is acellular rather than a lymphocytic infiltrate.

In their pathological report of patients with LINH Saito et al. [28] and Kojima et al. [29] described lymphocytic infiltration limited to the infundibulum, the stalk and the neurohypophysis [12]. Necrosis has been reported in some cases of LINH [14,26,48]

Clinical findings

Lymphocytic adenohypophysitis (LAH)

Most textbooks and classical descriptions refer only to this form of LYH, describing it as a disease typical of women during the peripartum period. In fact, LAH does occur more often in women, of whom 60% are diagnosed in relation with pregnancy, typically during the third trimester or in the postpartum period. A few cases have been described presenting during the second trimester of pregnancy [11]. The classical clinical picture includes: (i) headache and mass-effect symptoms (ii) symptoms of adenohypophysial hypofunction (iii) hyperprolactinemia, and occasionally (iv) symptoms of neurohypophysis involvement [1].

- (i) *Headache and mass-effect symptoms*: headache and impaired vision are the most common complaints and are reported in 50–70% of the cases [1,11,27,31,49]. Headache is a frequent manifestation of any pituitary conditions, and occurs as a consequence of functional or structural changes. It is now clear that even small pituitary lesions, with no apparent dural stretch or cavernous sinus invasion can cause headache due to incompletely understood functional disturbances [50]. In LYH headache tends to occur more frequently than in pituitary adenomas and it is often the first symptom, typically with a sudden onset. The location is bilateral frontal, retro-orbital or temporal [31]. Evidence of aseptic meningitis has been documented in LYH, which may represent an autoimmune reaction extension and could contribute to the reported high incidence and clinical features of headache in LYH [33]. Concomitant nausea or vomiting and fatigue are present in 25%, while weakness and anorexia are reported in about 15% of the cases [11]. In a review of 145 LYH cases by Beressi et al. [31] various visual disturbances were reported in 40% of the cases, the commonest being temporal hemianopsias and superior quadrantsias [34%]. Decrease in visual acuity was reported in 16% and diplopia in less than 10% of the cases [31,33].
- (ii) *Partial or total hypopituitarism* is found in 66–97% of cases [1,49] and may often appear disproportionate to the extent of changes on pituitary MR imaging, especially when compared with what usually happens in pituitary adenomas [33]. Interestingly enough, secretion of ACTH is the most frequently affected, reported in 60–65% of cases in the large series of Hashimoto et al. [12] and Beressi et al. [31]. Moreover, in LYH, ACTH deficiency has been reported even in isolation [51]. In contrast, ACTH is usually the last hormone to be affected in patients with pituitary tumors, a very important consideration in the differential diagnosis. In order of frequency, secretion of TSH (47%), gonadotropins (42.2%), GH (36.7%) and PRL (33.7%) may also be decreased [11,12].
- (iii) *Hyperprolactinemia* is reported only in 20–38% of patients. In some cases it can be ascribed to the associated pregnancy or postpartum period. In others cases, however, hyperprolactinemia is caused by stalk compression or by the inflammatory process itself, which may directly alter the dopamine receptors and the tonic inhibitory effect of dopamine on PRL release, or cause diffuse destruction of tissue and release of hormone into the bloodstream [1]. Some authors have suggested an autoimmune mechanism, involving the production of PRL-stimulating antibodies, analogous to what happens in Graves' disease [1,47,52].
- (iv) *Neurohypophysial involvement* manifested as DI of, in general, sudden onset, is seen in 14–20% of cases of LAH [1,11,12]. Nishioka et al. [17] reviewed the literature in 1996 and found 14 cases of histologically proven LAH with associated DI. Hashimoto et al. [12] found DI in 30 of 152 (20%) LAH cases. DI has been attributed in these cases to direct inflammatory invasion, destruction and/or compression of the posterior lobe or the pituitary stalk, or secondary to surgery [16].

Lymphocytic infundibulo-neurohypophysitis (LINH)

In cases of suspected LYH where DI is the presenting or most prominent symptom, diagnosis of LINH is most likely. Patients usually will also have mass-effect symptoms and may show evidence of other pituitary hormones deficiencies. In LINH, mass-effect symptoms have been described as limited to frontal or generalized headache and lethargy [5,14,25]. Only one of ten cases in a report by Miyagi et al. presented visual impairment [48]. The anterior pituitary function in LINH is frequently intact. When there is adenohypophysis involvement, it may be mild and often transient, involving most commonly GH [17,20,53], but also gonadotropins and thyrotropin [5,14,19,22,53]. Prolactin is usually normal or may be just slightly elevated [13,23,25].

Imura et al. [13] studied 17 patients with 'idiopathic diabetes insipidus' of 2-months to 20-years duration. Radiological findings in all, and histopathology in the two patients in whom biopsy was performed, was compatible with LINH. In addition to vasopressin deficiency, two patients had mild hyperprolactinemia and nine had impaired secretory responses of GH to insulin-induced hypoglycemia.

Lymphocytic infundibulo-panhypophysitis (LIPH)

The so-called LIPH has been reported especially in children and adolescents. These are cases of otherwise typical LINH but presenting with extensive and severe adenohypophysial involvement as well, evidenced both clinically and histopathologically [12,25,26,36, 53,54]. Whether these cases really represent a different clinical entity, involving different auto-antibodies, is not clear [49]. However, in order to better depict their clinical and pathological presentation, the term LIPH has been introduced by some authors. Hashimoto et al. [12] suggest that 10 of 30 cases of DI-associated LYH in their review would be more appropriately classified as LIPH.

Finally, it is noteworthy that in children and adolescents weight loss and fatigue appear to be in general more severe than in older patients [16,19,53]. Additionally, bone-age retardation has been observed in children [20].

Natural history

From the pathological point of view, the natural history of LYH is thought to progress from inflammation to fibrosis and subsequent atrophy, which can later present as an empty sella in imaging studies [22,55]. Spontaneous resolution has been reported by several authors [19]. Analogous to other autoimmune conditions, the initial inflammation with enlargement of the gland corresponds to the period of mass-effect symptoms and often, subclinical hormone deficits that can be exposed with appropriate dynamic testing. The ensuing progress to tissue destruction and atrophy is associated with permanent hypopituitarism [27]. In some cases the course of the disease can be rather insidious, and cases of relapsing-remitting LYH have been reported [56].

Similarly, in LINH the inflammatory process can be self-limited, and radiological follow-up can show regression in about 2-years time [13]. However, complete or partial CDI may be permanent, probably because of neuronal destruction [24].

Epidemiology

Eighty to 90% of the reported cases of LAH are women (5–8:1 ratio). Ninety percent of these women are premenopausal (<50 years) and, of these, 50–75% suffered the disease during the peripartum period [27,33,49,57]. The mean age at diagnosis is 34.5 yr for females and 44.7 yr for males [57]. No familial predisposition or ethnic preference has been described.

In contrast, LINH exhibits a balanced sex distribution, in some reports appearing even more prevalent among men; for instance there was 60% of males in the review of Miyagi et al. [48]. Other reports suggest that the representation of females in LINH is growing and by 1999, of the 40 reported cases reviewed by Takahashi et al. 70% were female [24].

The mean age in LINH is 47.3 ± 17.4 years. The youngest reported case was a 3-year-old and the oldest a 77-year-old [24].

Of note, many reports of idiopathic CDI, especially in the pediatric population might actually correspond to unrecognized cases of LINH. In a report, 6 out of 17 children with idiopathic DI had radiological evolution compatible with LINH [21]. Therefore the number of cases will probably continue to rise as clinicians' awareness increases and diagnostic criteria for these entities are developed.

Imaging studies

LAH

Radiological imaging may contribute objective findings in LYH. On plain films of the skull, the sella turcica has been

reported to be of normal size in about 40% of patients; it may appear enlarged in about 30%, and/or show erosion of its dorsum in 40% [32]. A flat floor, as oppose to the unilateral bulging more commonly seen in adenomas [58], is compatible with a diffuse inflammatory process such as LYH [55].

CT scan and MRI studies show an enlarging pituitary mass in 75–90% of patients, in case series presenting as LAH [1,6,9,11,32,49]. Even in cases where the initial scan may be normal, repeated imaging evaluations months later might evidence a mass-like image [32].

In a review of 63 patients, Heinze and Bercu [49] report *contrast enhancement* of the lesion in 70%. A marked contrast enhancement is considered to be common to other inflammatory processes of the pituitary gland as well [55]. However, a *triangular enhancement* of the anterior pituitary (reflecting extension of the process towards the pituitary stalk) along with enhancement of the *diaphragma sellae* (possibly reflecting inflammation by contiguity), although described only in a few cases, seems to be particularly specific of LYH; similarly, in this context, a ring-like enhancement is thought to be most consistent with central necrosis [55].

Suprasellar extension of the lesion is described in 62–75% of cases [9,11,32,49]. Honegger et al. [55] reported a tongue-like extension towards the hypothalamus as a characteristic finding both in lymphocytic and in granulomatous hypophysitis.

No tumor blush or abnormal vascularity has been described in the few cases where angiography has been done [29]. However, dynamic MRI has served to document a hypothalamic-pituitary vasculopathy in some cases. Sato et al. [10] performed dynamic MRI in 5 patients with either LAH or LINH and found *delayed of complete enhancement time of the whole pituitary* to more than 90 seconds (normal 60 seconds) in all patients. Only a part of the pituitary was enhanced even after 120 seconds in 4 patients. They also found delayed peak time of posterior pituitary enhancement (> 60 sec, normal 30 sec) in all patients.

LINH

In LINH, the radiological features are generally more clearly delineated. A diffuse thickening of the pituitary stalk is very characteristic, with a greater diameter exceeding 3.5 mm at the level of the median eminence of the hypothalamus [22]. On MRI, the normal smooth tapering of the infundibular stalk is lost and a varying degree of asymmetry may exist. Marked gadolinium enhancement of the stalk is quite common, extending even into lower hypothalamus. Loss of the usual neurohypophyseal “bright spot” is also commonly reported [13]. This spontaneous hyperintensity seen on MRI T1-W images in normal subjects is related to the phospholipid membrane

of the ADH-containing neuro-secretory granules. It has been showed that absence of the bright spot correlates closely with a loss of function of the neurohypophysis. However, it should be kept in mind that this MRI sign may be absent in ~ 10% of normal subjects [13].

In LINH, the anterior pituitary is usually of normal size and signal intensity [22]. In two cases reported by Shimono et al. [23] there was however swelling of the whole pituitary gland including the stalk, but not associated with appreciable anterior pituitary dysfunction.

LIPH

Extensive pituitary inflammatory changes have been reported in LIPH, extending upwards to the suprasellar area and affecting the optic pathway [26], or laterally to the cavernous sinuses [25].

Of 17 patients reviewed by Imura et al. [13], all lacked the neurohypophyseal bright spot of the normal neurohypophysis on MRI but, only 9, who had had diabetes insipidus for less than two years, had thickening of the pituitary stalk, enlargement of the neurohypophysis or both. These abnormalities disappeared during follow-up studies, suggesting that the process is self-limited.

Diagnosis

A presumptive diagnosis of LYH can be made based on clinical and laboratory findings and on imaging studies. Definitive confirmation requires histopathology, i.e. pituitary biopsy.

The clinician should suspect LYH, when evaluating a patient with evidence of pituitary dysfunction, if there is concurrence of 3 or more of the following scenarios:

1. Women presenting during the peripartum period.
2. Patients of young age (especially younger than 30 years old).
3. Isolated, early or disproportionate affection of ACTH or TSH secretion; and in general, disproportionate affection of anterior pituitary function for the magnitude of the changes on MR imaging.
4. Presence of other autoimmune conditions and/or positive autoantibodies, including thyroid peroxidase antibodies, antinuclear antibodies, antiparietal cells, adrenal antibodies, and antismooth muscle antibodies [30].
5. Acute onset of headache with mass-effect symptoms such as ophthalmoplegia, visual field defects, nausea or vomiting. Pituitary apoplexy may have a similar onset but it usually has a more catastrophic presentation, and distinct MR findings (pituitary hemorrhage). These conditions, however, are not mutually exclusive and, in fact, pituitary apoplexy can occur in a patient with LYH [59,60].

6. Acute onset of DI with headache and mass-effect symptoms, when granulomatous and infiltrative diseases like sarcoidosis and histiocytosis, which generally present more insidiously, can be excluded.
7. Presence in serum of antipituitary antibodies, where available.
8. Lymphomonocytic pleocytosis in the CSF, in the absence of clinical meningitis and antiviral antibodies.
9. Characteristic MRI findings:

a. For LAH and LIPH:

- (i) Intrасellar mass with marked contrast enhancement (triangular shaped and/or affecting the diaphragma sellae) or
- (ii) Diffuse, ill-defined, symmetrical pituitary enlargement (Fig. 1)
- (iii) Suprasellar extension, especially “tongue-like” extension
- (iv) Above scenarios with delay of complete enhancement time in dynamic MRI (>90 sec.)

b. In LINH (and LIPH):

- (i) Diffuse thickening of the pituitary stalk with or without enhancement after gadolinium (Figs. 1 and 2) and
- (ii) Loss of the normal posterior ‘bright spot’ on T1-weighted images (Fig. 3).

Although a definite diagnosis can only be established based on pathology findings, the effectiveness of a more conservative treatment approach in many cases [33] and the risks associated with pituitary biopsy or surgery, justifies attempts to develop clinical diagnostic criteria that could potentially obviate the need for invasive procedures unless urgent decompression is needed.

Interestingly, Pivonello et al. [61] using the Bayes theorem have showed, in patients with idiopathic CDI that it is possible to ascertain an autoimmune origin with an accuracy close to 100% using clinical, immunological and radiologic criteria. Idiopathic CDI was diagnosed when familial CDI, and CDI secondary to granulomatous disease, cranial surgery, trauma or tumors, were excluded. In this group of patients the probability of autoimmune CDI (ACDI) was defined as the likelihood of detecting circulating AVPCAb in serum. This likelihood was 33% in the whole group, but increased to 53% if age of onset was less than 30 years, and increased further to 90% if the patient had also another autoimmune condition. The probability of detecting circulating AVPCAb was of 99% if all previous criteria were met and in addition there was radiological evidence of pituitary stalk thickening.

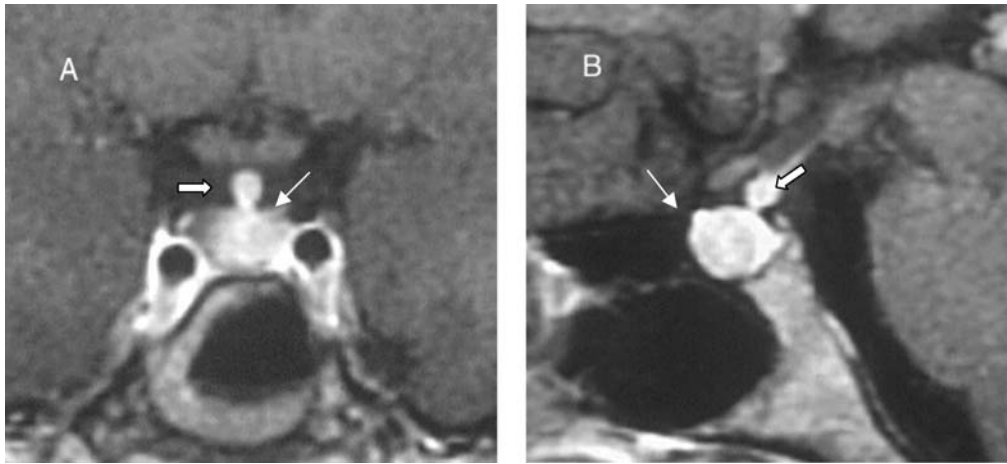


Fig. 1 Gadolinium (Gd)-enhanced coronal (A) and sagittal (B) T1 MRI of the sella turcica of a patient with LIPH. Narrow arrows point the markedly enhanced enlarged pituitary. Bold arrows point to a very thickened pituitary stalk

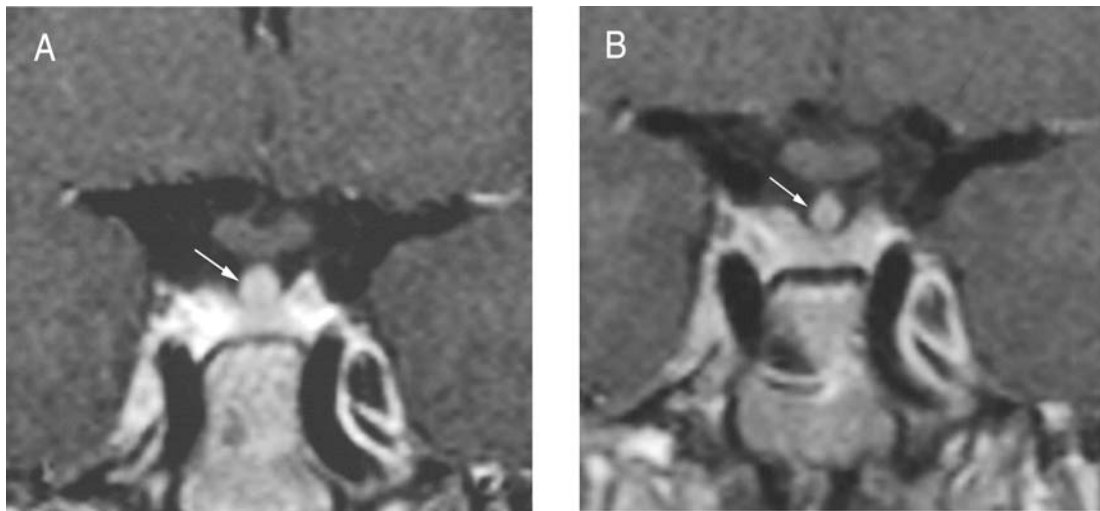


Fig. 2 Gd-enhanced coronal T1 MRI of the sella turcica showing enlarged pituitary stalk (arrows) in a patient with LINH at presentation (A) and 4 years later (B). Notice the significant reduction in size of the

pituitary stalk. The gland is otherwise normal and shows homogenous enhancement

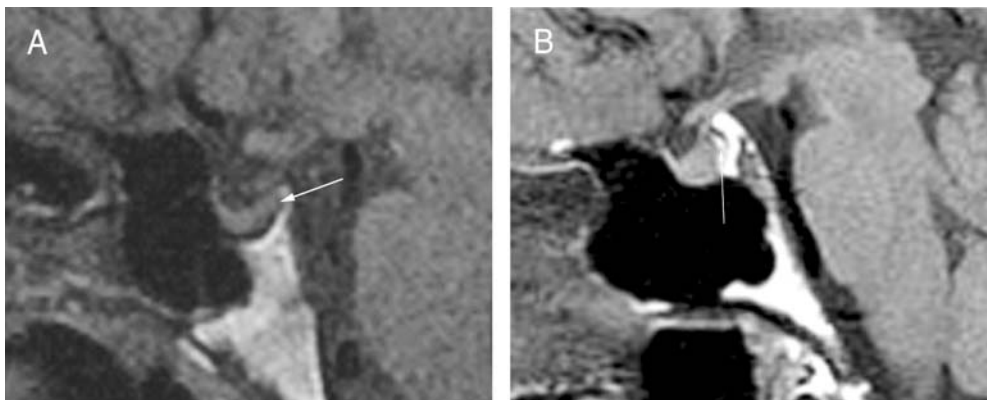


Fig. 3 Non-enhanced sagittal T1 MRI of the sella turcica shows (A) absence of the neurohypophysis hyperintense signal (arrows). For comparison a normal MRI of the sella turcica is shown (B)

At present, it is likely that most cases of suspected LYH with significant hormonal dysfunction and/or mass effect symptoms will end up necessitating tissue histology for definite diagnosis. Some have suggested transphenoidal stereotactic biopsy of the mass as a useful tool in the diagnosis of LYH in selected cases [62–64]. However, such procedures could be misleading by failing to obtain tissue from the actual lesion. For this reason some authors strongly encourage attempting whenever possible full resection of the abnormal tissue [7].

Differential diagnosis

The differential diagnosis of LYH includes pituitary adenomas and a large number of nonadenomatous lesions of the pituitary.

Although distinguishing LYH from *pituitary adenomas* can be very difficult, several distinctive features, some of which have already been discussed, should be considered. First, in functioning adenomas, clinical features of hormonal excess are usually evident at the time of presentation. Non-functioning pituitary adenomas, on the other hand, usually present in a rather insidious manner, either with mass effect symptoms (visual field defects) or with evidence of hormone deficiencies. Hypogonadism rather than hypocortisolemia or DI, is usually the initial problem in pituitary adenomas. A more acute presentation can be seen when pituitary apoplexy occurs in an adenoma. In this case MRI findings will usually be diagnostic. Sometimes, however the definite nature of the lesion is determined only after surgery, which has similar indications both in pituitary apoplexy and in LYH.

When LYH occurs in the postpartum period, *Sheehan's syndrome* needs to be ruled out. The later is due to apoplexy of the pituitary gland and can present abruptly or insidiously after delivery. Sheehan's syndrome is usually associated with obstetric hemorrhage and low prolactin with failure to lactate. It will very rarely present with DI, and is not associated with other autoimmune diseases.

Inflammatory pseudotumors are lesions with a broad spectrum of histological features, varying from a predominance of inflammatory cells mixed with some fibrous tissue to extensive fibrous lesions trapping some inflammatory cells. It has been described in the orbits, the lungs, upper respiratory tracts, head and neck, gastrointestinal and urinary tracts, as well as central nervous system and particularly in the pituitary [65]. In inflammatory pseudotumors, however, the inflammatory process is typically much more extensive, involving the sphenoid sinuses and the meninges (pachymeningitis).

Other primary hypophysitis, i.e. granulomatous and xanthomatous hypophysitis, are extremely rare disorders (annual

incidence of 1 in 10 millions or less) usually diagnosed in autopsy specimens. The clinical and radiological presentation is similar to LYH and the distinction can only be conclusively made by histological examination. For some authors they represent different manifestations of the same disease and, based on our current state of knowledge, their management is similar [57].

Secondary forms of hypophysitis should be carefully considered. These include: granulomatous hypophysitis associated with tuberculosis, syphilis and sarcoidosis; and a form of reactive hypophysitis sometimes seen in association with craniopharyngiomas and other sellar and perisellar tumors. The differential diagnosis here would focus on medical history (usually chronic and previously known disease), laboratory findings (tuberculin test and polymerase chain reaction in CSF for tuberculosis, treponema pallidum hemagglutination test for syphilis, and angiotensin-I-converting enzyme in plasma for sarcoidosis), and chest x-rays (tuberculosis and sarcoidosis) [33].

The differential diagnosis of LINH includes some rare tumors like germinomas and Langerhans' histiocytosis and can be very difficult. These tumors may present with DI and pituitary stalk thickening. However, the radiological findings are unlikely to regress; instead a rapid progression is seen in most cases. Histopathology is essential if such malignancies are considered.

Treatment

Glucocorticoids have been reported effective in LAH and LINH. Hashimoto et al. [11] reviewed 158 cases of LYH and found that 10 (62.5%) of 16 patients who received pharmacological doses of glucocorticoid (prednisone-equivalent dose ≥ 10 mg/day) showed reduction of pituitary mass. In contrast, 16 (44.4%) of 36 patients who received only physiological doses (prednisone-equivalent dose ≤ 7.5 mg/day) showed reduction of pituitary mass; the cure rate for hormonal disorders was also lower in this group. Kristof et al. [33] reported that high dose of methylprednisolone (120 mg daily for 2 weeks, followed by a tapering dose schedule (80, 60, 40 then 20 mg daily; 1 week per step) improved anterior pituitary function in 4 of 9 patients, and DI in all 4 patients presenting with this condition. The effect was more favorable in patients with short standing disease (less than 6 months) and improvement in MRI findings occurred in 88% of patients within 6 weeks to 6 months after therapy. In other reports the effect of corticosteroid therapy has been poor or transient and symptoms often returned after cessation of therapy [19,25,64].

Other forms of immunosuppression have been reported effective in specific cases with poor response to corticosteroids. Azathioprine [66], methotrexate [25] and

cyclosporin A [27] has been successfully used in isolated cases.

If symptoms do not improve with conservative management, transsphenoidal surgery for diagnosis confirmation and decompression is advised. A peroperative frozen section cytology should be performed to confirm the diagnosis and in order to avoid extensive unnecessary surgery. A pituitary experienced neurosurgeon would remove abnormal tissue and preserve normal-looking tissue to minimize the risk of hypopituitarism [35]. The surgical appearance of the lesions vary from soft yellowish to firm, fibrotic, whitish tissue, probably reflecting different stages of the inflammatory process at the time of surgery [55]. Immediate surgery may be necessary when there are signs of optic nerve compression or increased intracranial pressure [19].

Stereotactic radiotherapy has been used with success at controlling mass effect symptoms in 2 patients with LYH and severely affected pituitary function [64]. Although more experience with this therapeutic modality is necessary, it seems reasonable to say that it should be reserved for cases with severe mass effect symptoms, who show poor response or who are poor candidates for high dose of corticosteroids and/or surgery.

Conclusions

When discussing autoimmune inflammation of the pituitary gland (lymphocytic or autoimmune hypophysitis) it should be kept in mind that the condition alluded encompasses a spectrum of distinct clinical syndromes. Although certainly of seldom occurrence, LYH has very important diagnostic and therapeutic implications, considering that it is usually mistaken for tumors that may often require surgical management. The clinical presentation, concurrence of other autoimmune conditions and imaging findings can in many cases justify a vigilant approach, with or without glucocorticoid therapy and/or other immunosuppressant therapies. Specific serum markers are not currently available and are subject of research at leading centers around the world. Transsphenoidal needle biopsy has the potential to become a very useful diagnostic confirmation tool [63], but this method is neither standardized nor available in all centers. For this reason, it is expected that all potential cases of LYH be referred to centers where specialized neuroendocrine and neurosurgical care is available.

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