Lymphocytic hypophysitis

A review of 145 cases

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Lymphocytic hypophysitis (LH) is a new clinico-pathological entity, first described in 1962 by Goudie [46]. With recent advances in radiological investigation and technical refinements of trans-sphenoidal surgery, LH cases are being reported with increasing frequency. A total of 145 cases have been reported to date, 102 of them since 1990, with 121 histologically proven.

LH is an autoimmune endocrinopathy characterized by an extensive infiltration of the anterior pituitary gland by chronic inflammatory cells, which can cause pituitary expansion and a variable degree of hypopituitarism closely mimicking the features observed in pituitary adenoma. Involvement of the neurohypophysis rarely occurs in LH. The disease mostly occurs at the end of gestation or during the early post partum, but not exclusively: 23 cases of men and 13 cases of menopausal women have been reported in the literature. When no diagnosis is made, the sometimes insidious clinical course can progress towards hypopituitarism and can result in a lethal outcome. Better known since the last five years, clinical management remains a question of debate. Up to now, the majority of cases of adenohypophysitis were surgically treated leading to severe secondary endocrine deficiencies. Recently some authors (including in one personal case report) reported a new approach with corticosteroid therapy, which was successful in reversing the hypophyseal mass and the pituitary endocrine insufficiency.

**Pathological definition**

The definition of lymphocytic hypophysitis remains histological. In its classical form, adenohypophysitis is infiltrated, in a focal or diffuse way, by chronic inflammatory cells, chiefly lymphocytes and macrophages [159]. Sometimes neutrophilic and eosinophilic polymorphonuclear cells coexist with a variable degree of fibrosis. No microorganism is observed. Neurohypophysitis is usually spared by the disease, but in 8 cases, involvemnt of the infundibulum, neurohypophysitis, and pituitary stalk, by the same pathological lesion was observed [3, 108, 112, 158].

**Macroscopic findings**

The gland can be normal, grossly enlarged or atrophied. These different aspects are probably related to different stages of the natural course of the disease, similar to that observed in autoimmune thyroiditis. At trans-sphenoidal surgery, the gland is unusually firm, tough in its appearance and at palpation. The color varies from white or gray to yellow. When the lesion is encapsulated, it is wrapped in a dense pituitary capsule and if not, it appears adherent to the wall of the sella and is difficult to remove. Total extirpation of the mass is thus impossible in the majority of the cases [6, 81] as LH is difficult to shell out from normal pituitary tissue.
**Histological Criteria**

The anterior pituitary gland shows a diffuse lymphocytic infiltration seen in hematoxylin and eosin stain with a withdrawal of the normal pituitary architecture. This extensive cellular infiltration consists chiefly of lymphocytes accompanied by some plasma and mononuclear cells; a few spotted eosinophil cells has been even seen [3, 27]. While follicles with a germinal center can often be noted [6], no giant cell granuloma has been observed. The lesion is global, but mostly inhomogeneous in the majority of cases. The residual gland shows foci of uninvolved pituitary tissue which appears morphologically normal. Various degrees of edema and fibrosis are seen, but no adenoma feature is found and no microorganism is observed. The pituitary destruction is not confined to a particular cell type, as showed by immunocytochemical staining.

The lymphocytic infiltrate, studied by various authors [1, 6, 27, 40, 50, 51, 61, 66, 75, 83, 108, 119, 134], is made of activated T cells, with a dominant expression of CD4 marker (CD4+/CD8+, ratio 2:1) and macrophages expressing the MT1 marker [66, 83]. The predominance of T cells over B cells is in agreement with the characteristics of the infiltrate observed in other autoimmune diseases such as IDDM and Hashimoto’s thyroiditis [18, 32].

**Electron Microscopic Features**

The electron microscopic characteristics have been studied by various authors [1, 6, 50, 108]: in the most dense areas of inflammatory cell infiltration, pituitary cells show interdigitations with activated lymphocytes at their common interface. Some of these pituitary cells contain large lysosomal bodies fusing with secretory granules as well as an increased number of swollen mitochondria indicating a possible oncocytic transformation. No immune complex deposits are identified, and the vessels examined are usually normal.

**Pitfalls of Per Surgery Biopsy Analysis**

In general per surgery pathological analysis is not contributive. Diagnosis is usually fibrous adenoma [23, 54], normal hypophysis with rare lymphocytes infiltration [144], or non specific chronic inflammatory process. Diagnosis is even more difficult during the post partum period in the presence of lactotroph cell hyperplasia, which can mimic prolactinoma [10]. Nevertheless, in three cases [7, 81, 97] frozen sections gave the correct diagnosis, thus allowing limited surgery. Thus, the benefit of per surgery analysis seems to be limited.

**Diagnosis with Lymphocytic Infundibulo-Neurohypophysis (LINH)**

Lymphocytic adenohypophysitis and lymphocytic infundibulo-neurohypophysitis are distinctly specific entities, probably caused by different autoimmune processes [27, 51, 61, 83, 158]. In LH, diabetes insipidus (DI) is uncommon, and neurohypophysis has been reported to be histologically normal in most cases [27]. Unlike LINH, the inflammation is localized to the neurohypophyseal system and the disease is known to be a cause of central ID [61, 75, 163, 165]. In some cases, these 2 diseases seem to be dissociated: adenohypophysitis appears to be spared on MRI [61, 75] and histological biopsy [165] with features distinct from LH, but in some cases they may be concomitant events, with a sellar mass localized in the neurohypophysis associated with inflammation of the adenohypophysitis [109, 163].

**Clinical Findings**

Up to February 1998, 145 cases have been published in the English literature: 103 were diagnosed from surgical material, 15 were diagnosed at autopsy, 27 were not historically proven [37, 57, 161, 178]. Clinical, morphological, and radiological findings will be now discussed, as well as the evolution of medical and surgical treatment, following the presentation of a personal case, treated with success by corticosteroids [8].

A 27-year-old woman developed chronic headache 13 months after giving birth. Her pregnancy was unremarkable and she had a normal delivery. Persistent headache, associated with visual symptoms and amenorrhea, with galactorrhea led to a cranial CT-scan and magnetic resonance imaging (MRI). MRI revealed a markedly enlarged pituitary gland with a supra-sellar extension without any erosion of the dorsum sellae. Because of mild hyperprolactinemia, bromocriptine was prescribed at the dose of 5mg/daily and was soon followed by the transient appearance of menstruation. After two years of follow-up loss, panhypopituitarism was revealed by acute adrenal insufficiency, without hyperprolactinemia (table I). Magnetic resonance imaging showed that the pituitary mass was the same as previously described, with a superior triangular shape displacing the optic chiasm. A homogenous mass enhancement was observed after gadolinium injection (fig. 1A).

The occurrence of hypopituitarism with transient hyperprolactinemia a few months after pregnancy, associated with previously described radiological aspects led us to consider the diagnosis of LH. Nuclear antibodies were negative, as well as pituitary antibodies. Human leukocyte antigen serological class II typing was DR3/DR4. Because of the absence of any visual complications, and the patient refusal to surgery, prednisone was given at a daily dose of 60mg for three months, then progressively decreased for the next six months.

With this treatment, a clinical improvement consisting of disappearance of headaches and return of menstruation was observed. The biological feature showed a gradual recovery of all hormonal pituitary axis (table I). The MRI done after 3 months showed a substantial reduction of the pituitary mass reaching 70% after six month and sustained at 9 months (fig. 1B). Five months after interruption of steroid treatment, the patient relapsed with panhypopituita-
tarism and an increase of pituitary volume. Steroid therapy was resumed and a trans-sphenoidal pituitary biopsy was performed, confirming the diagnosis of LH. The patient still receives steroid therapy.

A SPECIFIC BACKGROUND AND ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

The disease shows a striking female predilection with a sex ratio of approximately 5.3 female for 1 male; it commonly affects young women during late pregnancy or the postpartum period, in two thirds of the cases. The mean age at presentation is 31 years in females compared with 42 years in males, with a range from 14 to 74 years.

Patients with LH are more likely to have other autoimmune diseases, as an association is found in 20% of cases (28 cases out of 145), principally with autoimmune thyroid diseases (82% of cases) [11, 46, 62, 66, 99, 102, 113, 118, 122, 135, 138, 148, 158, 167]. Other autoimmune diseases can precede or follow LH by a few years. LH is now part of the autoimmune polyendocrinopathies syndrome (APS) [101]. Among published cases, three cases of Addison disease were reported [78, 135, 140] including one associated with hypoparathyroidism [78] and one associated with retroperitoneal fibrosis and Hashimoto’s thyroiditis [148]; 2 cases of pernicious anemia were noted [58, 92], including one associated with Hashimoto’s thyroiditis [58], as well as 2 cases of Raynaud’s syndrome [34, 123], 1 case of IDDM and 1 case of autoimmune hepatitis associated with Hashimoto’s thyroiditis.

Idiopathic retroperitoneal fibrosis is a rare systemic autoimmune disease [74, 117, 130]. Fibrosis can occur in a few organs including the hypophysis [47]. In the case reported by Sobrinho [148], autopsy revealed a fibrotic case of autoimmune hepatitis associated with Hashimoto’s thyroiditis.

**Table I.** – Endocrine investigation before and after steroid treatment (60 mg/d) with prednisone during 3 months, then tapered for 6 months: baseline values and response of LH, FSH, ACTH, cortisol, and prolactin to the injection of LHRH, CRH, and TRH*.

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>June 1990</td>
<td>March 1992</td>
</tr>
<tr>
<td>LH (1-7UI/L)</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>Peak after LHRH</td>
<td>—</td>
<td>3.2</td>
</tr>
<tr>
<td>FSH (3-8UI/L)</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>Peak after LHRH</td>
<td>—</td>
<td>6.8</td>
</tr>
<tr>
<td>Estradiol (37-730pM/L)</td>
<td>—</td>
<td>68</td>
</tr>
<tr>
<td>TSH (0.2-4.5mU/ml)</td>
<td>0.88</td>
<td>5.9</td>
</tr>
<tr>
<td>Peak after TRH</td>
<td>—</td>
<td>8.8</td>
</tr>
<tr>
<td>FT4 (10-30pM/L)</td>
<td>11.8</td>
<td>1.4</td>
</tr>
<tr>
<td>ACTH (10-50pg/ml)</td>
<td>—</td>
<td>24</td>
</tr>
<tr>
<td>Peak after CRH</td>
<td>—</td>
<td>134</td>
</tr>
<tr>
<td>Cortisol (345-662nM/L)</td>
<td>—</td>
<td>32</td>
</tr>
<tr>
<td>Peak after TRH</td>
<td>—</td>
<td>107</td>
</tr>
<tr>
<td>Prolactin (130-700mU/L)</td>
<td>1440</td>
<td>376</td>
</tr>
</tbody>
</table>

* LHRH: luteinizing hormone; FSH: follicle stimulating hormone; ACTH: adreocorticotropic hormone; TSH: thyroid-stimulating hormone; TRH: thyroid releasing hormone; LHRH: luteinizing hormone-releasing hormone; CRH: corticotropin-releasing hormone; FT4: free thyroxine.

** After withdrawal of levothyroxine for 30 days, of prednisone for 15 days, and of hydrocortisone for 1 day.

Fig. 1. – a) coronal Gd-DTPA-enhanced, T1-weighted image (550/22/1) at the time of admission after gadolinium infusion. There is a large pituitary mass with a symmetrical extension and homogeneous enhancement. Compression of the optic chiasma by a suprasellar extension of the mass is seen. Note an unusually thickened and elevated diaphragma sellae as a discrete hypointense line outlined by the enhancement. b) Coronal Gd-DTPA-enhancement T1-weighted image, 6 months after therapy. The mass in the pituitary fossa has significantly decreased in size. Enhancement extends upward to a distal thickened stalk.
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infiltration of thyroid, adrenals and hypophysis. Concerned the endocrine organs with massive lymphocytic forming rare germinal centers. The other histologic lesions concerned the endocrine organs with massive lymphocytic infiltration of thyroid, adrenals and hypophysis.

Clinical presentation

Duration of the symptoms ranges from 1 month to 5 years, but the rather rapid onset of hypopituitarism can distinguish LH from adenomas. Most of the patients have completed hypopituitarism in less than one year, except in 5 cases whereas low course of two years [8,109,173] and five years [65, 123] was observed. The clinical presentation involves two categories of symptoms, those resulting from mass effects, which occur in 60% of patients, and the variable degree of hypopituitarism associated or not with hyperprolactinemia which is found in 85% of patients (table II).

Tumoral syndrome

The tumoral syndrome is characterized by its sudden occurrence and its rapid course. Headache and impaired vision are the most frequent symptoms reported. Headache is observed in 60% of cases; onset is noted during the third trimester of pregnancy and is exacerbated after delivery. Headache is localized to the frontal, temporal or retro-orbital region. Its frequency is higher than reported in adenoma [60, 93]. Various visual disturbances are observed in 40% of cases, including visual field defects, decreased acuity, blurring and diplopia. Among them a chiasmal syndrome, as temporal hemianopsia or superior quadrantanopsia, is found in 77% of cases [89]. A loss or decrease of visual acuity is observed in 40% [70], and 7 patients present diplopia arising from an extension of the process into the cavernous sinus with a sixth nerve palsy [2, 112, 156]. Acute degradation of blurring vision is often the reason for surgery emergency. Occasionally, aseptic meningitis or CSF leucocytosis is observed secondary to the pituitary lesion [56, 166]. CSF reaction, may represent an autoimmune reaction extending to the CSF space or a passive dissemination of inflammatory cells.

Endocrine disorders

Symptoms resulting from partial or complete anterior pituitary hypofunction are present in nearly 85% of patients. The degree of endocrine failure is not correlated to the radiological volume of the mass in opposition to the data found in pituitary adenomas. In patients with LH, hypopituitarism is present with small mass or even unenlarged pituitary, while in patients with tumor it is unusual to see such a degree of panhypopituitarism except when the mass is very large [27]. Biological panhypopituitarism is found in 32% of patients, after complete hormonal investigation (38 cases out of 117). The endocrine deficits are usually dissociated.

Gonadal function

In 40% of females (85% of affected subjects), the first clinical symptom reported is amenorrhea, the origin is variable. The association of amenorrhea and galactorrhea is not frequent, encountered only in 10% of cases, contrary to prolactinoma. As LH occurs mostly during pregnancy or postpartum period in 68% of affected women, an insufficiency in breast feeding was observed in 33% of these women (n=74). In males, biological hypogonadism is present in 82% of cases (19 cases out of 23).

Hyperprolactinemia

Despite the relatively low occurrence of amenorrhea-galactorrhea syndrome, hyperprolactinemia is found in 30% of patients with LH, galactorrhea was present only in 13 patients (12%) [25, 131]. Its interpretation remains controversial. Prolactin hypersecretion is a physiologic feature during pregnancy and postpartum period. In cases with expanding supra-sellar mass, hyperprolactinemia might be a consequence of the compression of the pituitary stalk, which prevents the inhibitory regulation of prolactin release by hypothalamic dopamine. But, as suggested by Bottazzo, the role of anti-PRL secreting cell antibodies could be comparable to what is observed with TSH receptor stimulating antibodies in Graves’ disease [15].

Adrenal axis

ACTH deficiency is the most frequent endocrine failure in patients with proven LH. Such deficiency is present in 65% of patient (n=141) and is responsible for the severity of the disease as in 12 patients death was directly related to acute adrenal insufficiency [34, 42, 43, 46, 58, 87, 88, 135, 139, 158]. Hypoglycemic comas were reported in 4 of these patients. The corticotrophin deficit was isolated in 14 cases [2, 37, 85, 102, 122, 135, 158, 167, 169]. Selective loss of corticotrop cells on histological study has been reported by few authors [66, 90, 135] and was well correlated with the clinical presentation of cortisol deficiency.

Table II. – Clinical features in lymphocytic hypophysitis (n=145).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Femal gender</td>
<td>84</td>
</tr>
<tr>
<td>Relationship with pregnancy or post partum</td>
<td>68</td>
</tr>
<tr>
<td>Post partum galactica</td>
<td>33</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>40</td>
</tr>
<tr>
<td>Tumoral syndrome</td>
<td>60</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>30</td>
</tr>
<tr>
<td>Anterior pituitary insufficiency</td>
<td>85</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>18</td>
</tr>
<tr>
<td>Associated autoimmune diseases</td>
<td>20</td>
</tr>
</tbody>
</table>

retroperitoneal mass involving iliac vessels, mainly composed of dense, sometimes hyalin collagen containing foci of lymphocytes clustered around vessels and forming rare germinal centers. The other histologic lesions concerned the endocrine organs with massive lymphocytic infiltration of thyroid, adrenals and hypophysis.

Table II. – Clinical features in lymphocytic hypophysitis (n=145).
Thyroid dysfunction

Clinical symptoms of thyroid dysfunction were observed in 18\% of patients with LH (26 cases out of 145). Autoimmune thyrotoxicosis episodes were noted in 10 patients, clinical hypothyroidism in 15 cases, and myxoedematous coma in one patient. A biological thyrotrhoph deficiency was found in 60\% of patients (71 cases out of 117). Among them, isolated thyrotrhoph deficiency has been described [84].

Somatotroph axis

The somatotroph axis has been rarely documented. Basal GH levels were low in 54\% of the patients tested (n=87). Insulin-induced hypoglycemia revealed a GH insufficiency in 17 cases out of 18 studied [13, 37, 40, 51, 77, 84, 90, 97, 100, 109, 111, 118, 119, 142, 176, 178]. In five of those, diabetes insipidus was associated with GH deficiency [61].

In men, a decreased libido and sexual impotence were the most frequently observed symptom. Endocrine investigation revealed 56\% panhypopituitarism (13 cases out of 23) and 82\% hypogonadism (19 cases out of 23).

Thus LH frequently result in isolated ACTH deficiencies or combined adrenal and thyrotrhoph deficits unlike endocrine failure patterns observed in non-secreting adenoma and Sheehan syndrome, where amenorrhea and somatotroph insufficiency are most frequent.

Neuro-endocrine disorders

Although it has been reported that diabetes insipidus is uncommon in LH, Thodou et al. reported it in 14\% to 19\%. To our knowledge, 26 cases were reported [1, 3, 26, 56, 63, 77, 99, 109, 113, 158, 173]. In these cases, thickening of the stalk and loss of T1 hyperintense signal of the posterior pituitary was frequently noted on MRI. Neurohypophyseal dysfunction may be attributed to direct inflammatory cell invasion, destruction or compression of either the posterior lobe or pituitary stalk.

Inflammation parameters

In the majority of published cases, parameters of inflammation were not documented. In 15 cases moderate increase in sedimentation rate (30/60mm/h) was observed [50, 56, 79, 118, 119, 132, 142, 148, 164, 176]. Lymphocytosis and eosinophilia were seen in one male case [49]. In a single case immuno electrophoresis showed an increased IgG and a slightly increased IgM ratio [148]. Lumbar puncure, detected lymphocytes in the CSF [56, 166] or an increased leukocyte count in the CSF [79], but in most cases results of lumbar puncure were normal [108].

Natural course of the disease

A total of 13 deaths were disease-related (acute adrenal insufficiency or hypopituitarism) [42]. Inversely, 19 spontaneous regressions of the mass have been also reported with sometimes a dissociation between the radiological resolution of the mass and non correlated partial or total recovery of adenohypophyseal function [12, 20, 24, 44, 60, 86, 94, 99, 113, 62, 118, 122, 123, 138, 158, 178]. Occasionaly, the pituitary may become strikingly and atrophic at the chronic stage [27] and may eventually cause empty sella syndrome [104, 113]; such a course was observed in 7 patients within a delay of 3 months to 6 years [62, 65, 99, 111, 113, 127]. Resumption of normal hormonal function is rare and does not correlate with the mass regression.

The long-term course of LH is not well documented. The disease course can be long. In our case [8], the tumoral syndrome was present with hyperprolactinemia up to two years before surgical procedure and hypopituitarism occurred progressively. Naik [103] reported a case of LH in which pituitary gland enlargement persisted for more than 10 years. In another case, reported by Nishokia [110], recurrence of LH occurred after a long free interval. A prompt corticosteroid treatment was dramatically effective on visual defect with significant reduction of the lesion on MRI. But the possibility of recurrence after steroid withdrawal was noted in a few cases reports [8, 90, 102].

These observations suggest that long-term follow-up with endocrinological and radiological examination is necessary for surveillance of patients with LH, as no predictive factors regarding the time course of the disease has been identified so far [120]. Nevertheless, it is important to underline that there is no early serological marker of the disease, as reported in IDDM and Hashimoto’s thyroiditis, which would be linked to the onset of the autoimmune process.

**LH and pregnancy**

No data on the natural history of the disease in a subsequent pregnancy is available so far. Six patients conceived spontaneously, three months to five years after diagnosis, with no apparent adverse influence of LH on pregnancy [11, 20, 66, 82, 83, 164]. Pregnancy did not have any adverse effect on the course of the disease. Moreover the resolution of the pituitary lesion was noted in one case [164]. LH should not be considered a contraindication to pregnancy if close neuro-ophtalmological and endocrine follow-up is planned [164].

**Neuroradiological findings**

The specific radiological abnormalities of LH may suggest the diagnosis before neurosurgical intervention.

**SKULL RADIOGRAPHS**

The pituitary fossa may be slightly enlarged [7, 50, 56, 90, 99, 124, 169], but surprisingly normal size is frequent even when the pituitary mass is relatively large. Minimal abnormalities may be observed: thinning or decalcification of the dorsum sellae without obvious ballooning. A flat sellar floor is mostly observed which contrasts with the unilateral depression generally found in pituitary adenomas.
MAGNETIC RESONANCE IMAGING (MRI) FINDINGS

Typical aspects of LH on MRI

Some MRI characteristics may help in LH diagnosis in the early, presumably active, phase of the disease, because they are quite different from those of typical pituitary adenoma and despite the physiologic pituitary enlargement that occurs during pregnancy [35, 45]. The first MRI was realized by Levine in 1988 for the diagnosis of LH. The pituitary mass has a suprasellar extension, displacing the optic chiasma upward in 64% of cases (77 cases out of 120) and showing a symmetrical and often triangular aspect.

The pituitary mass gives relatively low signal on precontrast T1 weighted images, and is iso-intense to gray matter. However a relatively high signal on T2 weighting may be a significant finding in LH, although not specific. Involvement of the cavernous sinus is rare, and was observed only in 7 cases [2, 112, 123, 156, 158, 169].

The posterior lobe is generally normal but the loss of hyperintense “bright spot” signal of the normal posterior pituitary on sagittal view [41], and thickening of the pituitary stalk have been reported in several cases of clinical DI [1, 2, 26, 61, 97, 109, 113, 138, 173]. Pituitary stalk enlargement and thickening, although not reported as classical radiological features of LH, were encountered in 15% of the cases (18 cases out of 120) [1, 3, 56, 79, 112, 113, 158, 166, 173]; in all the cases a stalk deviation was reported [137]. It is not clear, whether the stalk enlargement is a non specific reaction or an extension of the lesion along the pituitary stalk.

Gadolinium contrast enhanced MR images reveal an intense homogeneously triangular enhancement of the pituitary mass [2] associated with an abnormal dural enhancement, that seems to be pathognomonic of LH, it is described as a “dural tail”, consisting of strips of abnormal enhancing tissue along the dura mater. An abnormal enhancement along the posterior side of the infundibulum extending to the hypothalamus floor was also observed [2]. Extrapituitary components such as focal mucosa sphenoidal sinus enhancement consistent with an inflammatory reaction probably spreading from the pituitary fossa to the sinus [2, 3, 5] or involvement of the cavernous sinus were also noted [2, 112].

MRI in the differential diagnosis with adenoma

In adenoma the mass is on one side and not symmetrical. The stalk is not thickened, but often deviated. A low signal on precontrast T1 weighted images is uncommon in solid pituitary macroadenomas [2, 138]. In the case of macroadenomas, a posterior pituitary lobe may occasionally be seen, but is often deformed or displaced. After injection of gadolinium, pituitary adenoma usually shows only moderate enhancement. Occasionally, a ring-like enhancement consistent with a central necrosis aspect is observed in pituitary adenomas complicated by hemorrhage, necrosis, or infarction. These aspects are rare in LH and were reported in only 5 cases [21, 56, 64, 164, 169]. In opposition to the LH “dural tail”, no enhancement of the adjacent dura mater is observed in most cases of pituitary adenoma [2].

The lack of specificity of images

Any inflammatory mass has interstitial spaces and increased water content in the acute phase of inflammation, explaining relatively low signal on T1 weighted images and less mass effect on adjacent structures than a solid tumor. Pituitary stalk enlargement and thickening are also observed in neurosarcoidosis and are probably due to inflammation, hyperemia and stalk edema. Marked enhancement, as typically found in inflammatory lesion of the pituitary [156], can be attributed to the increased interstitial space with free diffusion of contrast medium into the extra cellular space, where an increased number of water protons is available [138].

Pathogenesis

CLINICAL BACKGROUND

The autoimmune nature of LH is supported on the presence of typical pathologic inflammatory features, circulating organ specific autoantibodies and other coexisting autoimmune diseases [15, 101]. For various authors, LH is part of the type I autoimmune polyglandular syndrome [69, 101, 106]. Various clinical, biological, experimental and anatomicopathological evidence [39, 67, 121, 125, 151, 171] favors the autoimmune origin of the disease.

High incidence of the disease during the third trimester of pregnancy or in the post-partum period are in favor of an autoimmune process [5]. The alteration of the immune system during this period explains the exacerbation of autoimmune disease (AID), as observed in lupus erythematosus [149]. Various hypotheses concerning the mechanism have been proposed: decreasing levels of helper T cells with loss of immune surveillance and self recognition [171], or loss of “fetal suppressor factor” in the post-partum period which allows an autoimmune reaction to occur. Therefore in cases with temporal relationship to pregnancy, symptoms may worsen in the post-partum period.

The coexistence of lymphocytic hypophysitis with other autoimmune disorders (AID) is found in 20% of the 145 cases described, as already emphasized by Cosman [27] and Lee [79]. The most frequent associated AID are thyroid autoimmune disease (cumulating cases n=21) such as Hashimoto’s thyroiditis, post partum thyroiditis, painless thyroiditis or Graves’ disease. Another prominent feature of AID is the presence of autoimmune multiple organ failure found as Biermer anemia, Addison disease, primary hypoparathyroidism, and insulin dependent diabetes mellitus (IDDM) in the same individual [43, 46, 58, 78, 135].

In the few cases where the major histocompatibility complex (MHC) class II antigens were studied (17 cases), class II typing was DR4 (41%), as usually observed in other AID [8, 53, 123, 150, 156, 176]. DR5 was also
Lymphocytic Hypophysitis

Experimental models

Experimental animal models have been useful in showing that LH is a transferable autoimmune disease:

– Triplett observed that LH can be induced by the reimplantation of autologous pituitary tissue in frogs, after surgical removal. In this model, the pituitary graft was acutely rejected and the pathological analysis of the reimplanted tissue showed comparable results as the one observed in LH. These results are in favor of a loss of tolerance after primary removal of the pituitary [162].

– Levine [80] has, in 1967, used a model of adenohypophysitis induced by the subcutaneous injection in rats, of pituitary anterior lobes homogenates, with complete Freund’s adjuvant. In this model, LH is observed two to three weeks after the injection of homogenates and seems limited to the pituitary, sparing other endocrine glands. The pituitary cellular infiltrate is made of mononuclear cells, monocytes, lymphocytes and a few epithelioid cells. The disease appeared more severe in a small subgroup of pregnant and postpartum rats and has been related to the hypervascularization of the pituitary gland during this period as well as to high estrogen levels.

– Klein [71] has used rabbit females injected with homologous pituitary homogenates with adjuvant. Out of the seven animals, five developed a lymphocytic infiltration limited to the anterior pituitary gland. Four affected rabbits had a positive lymphoblastic transformation test in presence of pituitary tissue in vitro. Interestingly, the severity of the infiltrate correlated with the level of radioelement incorporation during the transformation test. But in vivo no circulating pituitary autoantibodies were found in immunized rabbits serum.

– Rubella virus has been used as a triggering factor inducing LH in the animal model of Yoon [177]. In the Syrian hamster, the injection of Rubella recombinant glycoproteins, E1 and E2, is followed after two weeks by the appearance of LH in 50% of the animals studied and the production of antibodies directed towards pituitary cells. Furthermore, the disease is prevented by neonatal thymectomy, suggesting the role of T lymphocytes at the origin of disease.

All these results are consistent with the role of an autoimmune reaction in the genesis of human lymphocytic hypophysitis.

Role of pituitary autoantibodies

In many endocrine autoimmune diseases, serum autoantibodies (Ab) act as serological markers of the disease. But anti-pituitary Ab set up a particular problem because the assay is difficult to perform, its sensitivity is low and its specificity and predictability in LH are poor. The multiplicity of target auto-antigens used for the assay, because the specific one is still unknown, makes the assay not as reliable as the other antibodies used in autoimmune endocrine diseases as IDDM, Hashimoto’s thyroiditis and Graves’ disease.

Techniques

The first description of Ab directed against the pituitary was made by Engelberth and Jezkova in 1965 [36]. These authors used complement consumption test, with homogenate prepared from anterior lobes of human pituitaries. They tested the serum of 128 post-partum women three times: at the end of pregnancy, at delivery, and at the fifth or seventh day after birth. The Ab became positive only after five days in 18% of parturients. Among them, 25% progressed towards adenohypophysis insufficiency, versus 4% in the group without Ab. Since this first description, multiple techniques have been described, but the specificity and sensitivity of the methods were not always clearly defined (table III). The most widespread techniques are the indirect immunofluorescence assay using, in initial experiments, unfixed frozen section of fresh human pituitary gland obtained at hypophysectomy for advanced carcinoma of the breast [36], followed by techniques using rat pituitaries [126], and in recent publications, cultured rodent pituitary-derived cell lines (corticotrophin secreting mouse AT20 cell and GH-PRL secreting rat GH3 cells) [153, 154]. According to the technique used, Ab directed against all varieties of pituitary cells (PRL, GH, ACTH), may be found, the prolactin-secreting cell being the predominant type.

Therefore, as it depends on the type of techniques used, the interpretation of the published results is difficult.

Sensitivity

Because circulating antipituitary Ab measurement is difficult to perform and not routinely available, Ab were detected in only a minority of patients with LH: among the 145 cases reported in the English literature, 38 were tested for pituitary Ab and 8 (21% of cases) were positive [19, 62, 44, 90, 111, 118, 142, 174]. Sugihara noted that the presence of Ab against pituitary depended on the technique used [153]. Moreover the sensitivity seems to decrease when human pituitary tissue is used [126]. Out of 18 IDDM patients, the percentage of anti-pituitary Ab varied from 16.7% to 66.7% depending on the type of the pituitary cell line (respectively GH3 and AT20) used for the assay [154]. However, a longitudinal study [68] in patients with hypopituitarism indicated that anti-pituitary Ab titers fluctuate and may disappear during the course of the disease without any improvement of pituitary function. Interestingly in this same study, Ab were also found in patient relatives, suggesting a hereditary background for such autoimmune disease.
Specificity

In addition to the previous unsolved technical problems, pituitary Ab appear to be less specific or predictive of the LH than other antibodies in autoimmune endocrine diseases as IDDM, Hashimoto’s thyroiditis and Graves’ disease.

They have been found in various non autoimmune pituitary diseases: pituitary adenoma [76, 126], Cushing’s disease prior to surgery [141], Sheehan syndrome [36], empty sella syndrome [76], isolated growth hormone deficiency [28], and idiopathic hypopituitarism [68]. Komatsu in 1988 [76] showed, in 75% of 32 patients with primary empty sella syndrome, the presence of pituitary Ab using indirect immunofluorescence with AT20 cells and in 47% using GH3 cells. No correlation with hypopituitarism was found in these patients. The frequency of positivity for pituitary Ab was still higher in patients with the empty sella syndrome than in patients with pituitary adenoma (12% and 16%, respectively with the two methods) or diabetes insipidus (33% with the two methods). In 1980, Bottazzo et al. [16] investigated 483 children with various growth disorders, and 6% of the sera reacted with isolated pituitary cells. Thus, despite some methodological restrictions, the presence of pituitary Ab seems to be correlated with an evolution towards hypopituitarism only in the post-partum period [36, 95]. It remains unclear whether these Ab have any diagnosis or predictive value for hypopituitarism, as there is still no definite correlation between the presence of pituitary Ab and a corresponding pituitary hormone deficiency.

Pituitary Ab can even be found in the absence clinical pituitary disease, as in patients with other autoimmune diseases. The presence of anti-prolactin cell Ab is observed in 7% of the serum of patients with autoimmune polyglandular disease associated with primary hypoparathyroidism, but without evidence of pituitary dysfunction [14]. Bottazzo and Doniach [17, 96] found that 15% of the sera of 118 patients with IDDM had anti-prolactin cell antibodies. In recent study, Kobayashi et al. [73] found a frequency of pituitary Ab higher in IDDM (56%) and non IDDM (24%) patients than in healthy control subjects (6%). Similar results were found in patients with Hashimoto’s thyroiditis and Graves’ disease [72, 155].

Identification of the target autoantigen

Bottazzo et al. [14], showed that pituitary Ab were directed against a cytosolic fraction involved in the synthesis and transport of hormone rather than the hormone itself. Yabe et al. [175], showed evidence by Western blot analysis that the sera from 6 patients (which showed various staining patterns by IF methods) reacted with various components of the rat pituitary membrane and cytosolic fraction of different molecular weight (the 97.5 kDa, 65 and 47 kDa bands correlated to one staining pattern) reflecting possible different pituitary antigens. Only anti-ACTH antiserum recognized several bands between 22-110 kDa; other specific rat pituitary hormone Ab (LH, FSH GH) did not recognize rat pituitary antigens. Recently, Crock [28] reported the detection of anti-pituitary Ab, by immunoblotting with human pituitary tissues as antigens. A 45 kDa pituitary specific membrane protein was identified as an autoantigen in one of 19 patients with idiopathic growth hormone deficiency and associated with an empty sella syndrome. A 43 kDa, pituitary and brain membrane protein was identified as an autoantigen in two patients with growth hormone deficiency.

Thus, the exact role of the Ab in the pathogenesis of LH remains largely unknown. Unlike the passive transmission of AID by serum such as experimental myasthenia [160] or experimental autoimmune thyroiditis [170], data concerning experimental hypophysitis do not demonstrate an important role for pituitary autoAb in pathogenesis of LH [177]. Contrary to other AID, sensitivity and specifi-

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Antigen used</th>
<th>Cell target</th>
<th>Method</th>
<th>Clinical context</th>
<th>% positive</th>
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<tr>
<td>Engelberth</td>
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<td>complement consumption test</td>
<td>Sheehan syndrome (n=128)</td>
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<td>prolactin</td>
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<td>GH3 (rat)</td>
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<td>IDDM (n=18)</td>
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<td>AT20 (mouse)</td>
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<td>ACTH deficiency (n=5)</td>
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<td>immunoblotting (titres up 1/1000)</td>
<td>secondary GH deficit (n=14)</td>
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</table>

Table III. – Techniques of anti pituitary Ab assay.
city of pituitary Ab do not allow early diagnosis of the disease as in IDDM, and do not shed light on the natural history of the disease.

**Management and treatment**

As the natural course of the disease, seems variable and sometimes of long duration, the management of LH remains controversial.

**Surgery**

Two-thirds of the published cases underwent surgery because preoperative diagnosis was pituitary adenoma with chiasmal compression. After surgical removal of LH, recovery of hormonal pituitary deficiency is rare. Surgery is deleterious on the endocrine function since approximately one third of operated patients have total or partial post-surgical hypopituitarism requiring hormonal replacement. Except when partial removal or limited biopsy of the lesion was performed, allowing in some cases a favorable outcome, pituitary function improved in only 15% of cases after surgery [83, 86]. Honneger [56] noted that no recurrence was reported after radical surgery leaving the patient with anterior pituitary insufficiency. Nishokia [110] estimates that LH surgery should be performed only when mandated by the presence of visual impairment or other potentially irreversible neurologic signs, when progression of the mass is rapid despite corticosteroid therapy or when atypical symptoms such as ID or sinus cavernous involvement are present.

**Medical treatment**

**Bromocriptine**

Bromocriptine has been used for treatment of hypophysitis misdiagnosed for prolactinoma in patients with hyperprolactinemia [6, 13, 21, 40, 83, 84, 85, 112, 123, 127, 134, 150, 158, 166, 169, 174]. Various results have been observed in this small group of patients (17 cases) such as normalization of prolactinemia, or reversed galactorrhea and amenorrhea. In three cases only, an improvement of visual field defects was observed [6, 84, 158].

**Corticosteroids**

The use of corticosteroids appears to be the logical treatment of hypophysitis as it as been used with success in various autoimmune diseases. Thirty patients underwent such a treatment in the literature [8, 145]. Results are not always available, but a benefit on the visual symptom or headache and a decrease of tumoral size have been observed in 18 cases. An impairment of hormonal pituitary function was noted for 7 patients, whereas it should be pointed out that most of cases showed a recurrence of disease after tapering or withdrawal of corticosteroid [3, 8, 56, 112, 123]. Duration of treatment and doses used are not the subject of a general agreement, however high doses (2 mg/kg) should be preferred in order to quickly evaluate the response to such therapy. Although its efficacy in this disease remains uncertain [108, 134, 158] conservative treatment with corticosteroids has been recommended when there is no gross visual disturbance [2, 8, 12, 27, 40, 128, 150]. Corticosteroids seem also the most logical treatment of LH occurring during pregnancy or post-partum, where the disease may improve late after pregnancy.

**Other immunosuppressive drugs**

Others immunosuppressive drugs such as cyclosporine or FK506 (Tacrolimus) have not been used in the treatment of LH. Their potential benefit in the treatment of the disease has yet to be demonstrated.

**Surveillance with hormonal replacement alone**

The natural history of autoimmune hypophysitis suggests that the inflammation would eventually subside. The case of Brandes [20], reporting a 17-year old female whose pituitary mass with supra sellar extension and anterior pituitary deficiency regressed to an empty sella over 5 years, illustrates that abstention might be mandatory, except in the presence of progressive visual impairment. Moreover, spontaneous radiological resolution, during short term follow-up has been well documented in the literature (16 cases) [24, 60, 86, 108, 113, 116, 158]. An evolution toward empty sella syndrome, noted in 5 cases further justifies this attitude. In case of presurgical imaging diagnosis, complete antehypophyseal surgical resection should be avoided because of the self-limited course of the disease, especially if vision is not compromised [8, 128].

**Differential diagnosis**

Review of the literature indicates that the principal misdiagnosis is prolactin secreting pituitary adenoma or non-secreting adenoma [7, 27, 59, 81, 90]. Preoperative diagnosis between these two entities is necessary as already discussed, and can be suggested on the basis of endocrine and MRI features. The distinction is mandatory because of specific therapeutic issues (surgery or medical) in each diseases, since in LH extensive resection may exacerbate the often preexisting hypopituitarism [27, 81]. Pituitary abscesses are rarely confusing with LH, as background and radiological findings are different. The clinical symptoms of pituitary abscess typically include hypopituitarism and sometime visual disturbances, with at MRI a cystic formation, which can be misdiagnosed as Rathke’s cleft cyst or cystic pituitary adenoma. In the majority of cases, pituitary abscess develops in a setting of bacterial meningitis, sinusitis, sepsis or immunosup-
pression. Some cases develop as a late complication after pituitary surgery [105]. Pituitary abscess was also described in association with craniopharyngioma [114], Rathke’s cleft cyst or pituitary adenoma [105]. In these cases the previous necrosis of the tumor may induce the pituitary abscess formation [105].

Specific granulomatous hypophysitis (SGH) is characterized by the presence of a granuloma, made of multinuclear giant cells and histiocytes with epithelioid cells in response to systemic syphilis, tuberculosis, sarcoidosis or histiocytosis X [30, 31, 107]. In the serie of Rickards [136], out of 113 autopsy cases of hypophysitis granuloma, 23 were a specific granulomatous hypophysitis. In SGH, a general inflammatory syndrome is present, and pituitary symptoms are not isolated but are associated with specific abnormalities of chest X-ray, biological inflammatory syndrome, including increase of sedimentation rate, increased polyclonal serum gammaglobulins, and increase of serum angiotensin-converting enzyme (ACE).

In sarcoidosis, central nervous system is involved in 5 to 5% of the reported cases and is exceptionally the only sign [22, 91]. The inflammatory infiltrate, reaches the neurohypophysis in 90% of cases, inducing diabetes insipidus (DI) [152]. One case of LH associated with pulmonary and eye sarcoidosis was reported, but no histological feature of sarcoidosis was observed in the pituitary [53].

Sellar tuberculosis is today extremely rare in clinical practice. Three cases have been reported by Esposito [38], and Berger [9] reported a series of 9 well documented observations. Recently Ranjan [133] reported five patients with biopsy proven intrasellar tuberculosis with suprasellar extension. In these cases the triad of headaches, fever and visual symptoms was present. Endocrine insufficiencies were usually dissociated and might occur, a few years after the initial episode of acute meningitis. Moreover calcifications of hypothalamic region were frequent [29].

Idiopathic granulomatous hypophysitis (IGH), identified by giant cells, was first described in 1917 by Simmons [146]. It has been rediscovered for several years, but remains not well known [3, 52, 143, 157]. Clinical evaluation must exclude specific granulomas (sarcoidosis, tuberculosis or fungal infection). The prevalence of the disease is low, approximately 28 cases being reported in the literature [33, 115, 140]. Various findings differentiate this disease from LH: there is no sex ratio in favor of female, it does not occur during pregnancy and there is no relation with an autoimmune process [168]. Moreover, DI seems frequent, in opposition to LH, but only pathological analysis can establish the diagnosis. However idiopathic granulomatous hypophysitis and lymphocytic hypophysitis have been associated in 2 cases [56, 98]. Furthermore, ultrastructural studies by Mc Keel [87] raise the possibility that the two disorders are related. The agent responsible for the formation of granulomatous elements remains uncertain, but the relatively frequent association of giant cell hypophysitis with other chronic pathological processes involving the parasellar region, chromophobe adenoma [55], Rathke cyst [4, 172], sphenoidal mucocele [140] suggests that the inflammatory cells might be seen as a manifestation of a granulomatous foreign-body type reaction.

Recently Sautner has reported [139], a new classification of pituitary inflammatory diseases, which account for 0.5% of the sellar diseases, introducing “secondary hypophysitis” as a new entity. Secondary hypophysitis consists of inflammatory extension into the pituitary gland from a tumor localized in the sellar region. As noted by a few authors [4, 55, 82, 129], the origin of the mechanism leading to hypophysitis seems to be clearly different from LH or granulomatous hypophysitis. In secondary hypophysitis, the affected area is composed of fibrous tissue and granulation tissue, B and T lymphocytes are present in equal amount, and there is no granuloma.

**Conclusion**

Lymphocytic hypophysitis is a rare autoimmune lesion of the pituitary gland, histopathologically characterized by lymphocytic infiltration and destruction of the anterior pituitary. Nearly 145 cases have been reported since the first description of the entity in 1962 by Goudie [46]. Patients may present with symptoms of an expanding intrasellar mass or with varying degrees of pituitary dysfunction. 84% of affected subjects are female and two thirds of cases occur during pregnancy or postpartum period. Adrenal and thryeotroph insufficiency are the most frequent endocrine failure, whereas the gonadotrop axis is relatively preserved. An important element of diagnosis is the radiological aspect consisting of a symmetrical pituitary mass, with gadolinium homogeneous enhancement. Despite the diagnosis can be suspected from the medical history and imaging studies, biopsy is necessary if a trial course of steroid therapy fails. The surgery should be limited to a biopsy only or if needed to decompress the optic chiasm. The natural course of LH is still imprecise but spontaneous regression of intra sellar mass is not infrequent, thus favoring the hypothesis that some apparently idiopathic pituitary insufficiencies or empty sella turcica may in fact be the final term of initially undiagnosed LH.

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