Lymphocytic hypophysitis - A case report

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Abstract

Lymphocytic Hypophysitis (LH) is the most common variant of primary hypophysitis, which is a rare condition itself. LH is a rare inflammatory/autoimmune disease of the pituitary gland and the stalk. The authors present this case given its rarity, and difficulty to diagnose, and atypical presentation. The case refers to a 36-years old female, 2 pregnancies, 2 childbirths, who at the 10th gestational week of the second pregnancy complained of frontal headaches with decreased visual acuity on the left eye. The patient went to the emergency department for clinical evaluation, having been admitted and observed by neurology and ophthalmology departments for five days. No radiological tests were carried given the situation, having been medicated with paracetamol, with no diagnosis. The patient was discharged with no headache complaints, although a slight visual impairment. A year after childbirth, she starts complaining of frontal headaches again, which irradiate to the left orbit, and slow pupil reflexes, having been observed by the department of ophthalmology that asked for a brain and orbit MRI that showed a suspicion of Rathke pouch cyst and possible lesion to the optic chiasm. After discussing with a multidisciplinary team, it was decided to proceed with a left pterional approach to puncture the cyst. The tissue removed was sent to pathology for histological study. The resulting diagnosis is compatible with LH, namely fibrous connective tissue with glandular structures from the adenohypophysis, with a mild to moderate lymphocytic inflammatory infiltrate, with no signs of neoplastic development. The patient status improved significantly post-surgery with no need for therapy. After 6 months, the patient remained clinically stable. A high degree of suspicion is necessary between clinical, laboratory and radiological findings to diagnose LH and avoid unnecessary treatment. Glucocorticoids therapy is recommended if the lesion is diffused or just suprasellar, or if the symptoms are less severe, however, it should be taken into account the risk of adverse effects and recurrence. Surgery helps the differential diagnosis and relieves compression symptoms.

Keywords: Lymphocytic hypophysitis, Autoimmune diseases, Pregnancy, Visual impairment, Glucocorticoids.

Accepted on September 10, 2020

Introduction

Lymphocytic hypophysitis (LH) is the most common variant of primary hypophysitis, which is a rare condition itself [1]. LH is a rare inflammatory/autoimmune disease of the pituitary gland and the stalk [2]. Once underdiagnosed, today it is increasingly recognised, and the diagnosis is based on histological confirmation [3]. LH's aetiology remains unclear [4] and has an estimate incidence of 1 in 9 million/year [5]. It should be considered in the differential diagnosis of pituitary masses and/or hypopituitarism in pregnant women or in a recent postpartum period [6]. It can affect both genders and all ages [2], being more frequent in women, a common trait with several other autoimmune diseases, presenting itself between the 4th and 5th decade in women and men, respectively [1]. Clinical presentation depends on the pituitary segment affected. There is no specific serological or biochemical test for this type of hypophysitis [7], which makes its diagnosis a challenge. The diagnosis is confirmed histologically [1] and should be suspected when there is a rapid onset of hypopituitarism with low secretion of Thyroid-stimulating hormone (TSH) and/or Adrenocorticotropic hormone (ACTH) and a normal growth hormone [GH] and gonadotropin profile, and the magnetic resonance imaging [MRI] shows a lesion with a diffuse contrast enhancement with gadolinium in a pregnant woman or postpartum [7].

The treatment is controversial; it is important to have a clinical and radiological substantiated suspicion in order to make decisions. An initial treatment of hormone replacement may be necessary. The cornerstone of treatment is glucocorticoids; for those who don't respond or present side effects the use
of immunosuppressants like azathioprine, methotrexate and cyclosporin A has shown positive results. Surgery is recommended for those non-responding situations, mass effect, visual impairment or when the tissue is relevant for diagnosis [2].

**Case Report**

The case refers to a 36-years old female, white, a teacher, previously healthy, 2 pregnancies, 2 childbirths, who at the 10th gestational week of the second pregnancy complained of frontal headaches with decreased visual acuity on the left eye. The patient went to the emergency department of another institution for clinical evaluation, having been admitted and observed by neurology and ophthalmology departments for five days. No radiological tests were carried given the situation, having been medicated with paracetamol, with improvement of the symptoms but without clinical diagnosis. The patient was discharged with no complaints of headache, however, since a mild visual deficit persisted, she was given a prescription for glasses, which the patient didn't comply with. There were no clinical changes for the remaining period of pregnancy. Natural birth at 39 weeks, with no complications. The patient breastfeeding for 4 months. A year after childbirth, she starts complaining of frontal headaches again, which irradiate to the left orbit, and slow pupil reflexes, having been observed by the department of ophthalmology. Further examination revealed an uncorrected visual acuity of 10/10 in the right eye and of 8/10 in the left eye, and campimetry demonstrated a deficit on the left eye [LE]. An MRI of the brain and orbit (Figure 1) revealed an expansive intra- and suprasellar lesion, oval configuration, with high signal intensity on T1, T2 and FLAIR, highlighting a nodule on its lower median side, with the highest signal on T1 and lower signal on T2 with $17 \times 19$ mm. These characteristics suggested a Rathke pouch cyst. The lesion was more marked in the suprasellar cistern, especially on the left, affecting the superior bulge and deforming the optic chiasm and the pre-chiasmatic segment of the optic nerve. Although some structures on the left didn't present signal changes on T2, there were conditions in place that indicate they may also have been affected.

The ophthalmologist referred the patient to the endocrinology department in our institution. Here, we carried additional analytical exams (Figure 2) that didn't show hormonal changes nor changes associated to autoimmune diseases. The patient was referred to the department of neurology under suspicion of Rathke pouch cyst and possible lesion to the optic chiasm. After discussing with a multidisciplinary team, it was decided to proceed with a left pterional approach to puncture the cyst. A total of 2 ml of yellow dense fluid was drained and part of the membrane was removed with no complications. The tissue removed was sent to pathology for histological study. The resulting diagnosis is compatible with LH, namely fibrous connective tissue with glandular structures from the adenohypophysis, with a mild to moderate lymphocytic inflammatory infiltrate, with no signs of neoplastic development.

The patient status improved significantly post-surgery with no need for therapy. After 6 months, the patient remained clinically stable.

**Discussion**

Hypophysitis is an inflammation process of the pituitary gland, which can be classified according to the anatomic location involved. There are two forms: the primary, which develops intrinsically to the pituitary gland, and the secondary, which is associated to systemic diseases, infectious processes and/or drugs [8-12]. Primary hypophysitis can be divided into five types: lymphocytic, granulomatous, xanthomatous, IgG4-related, and necrotising [1].

LH is an inflammatory disease that mostly affects the anterior pituitary gland (lymphocytic adenohypophysitis), like the case described above, but it can also affect the posterior pituitary gland and the infundibulum (infundibulo-neurohypophysitis).
A rapid onset of hypopituitarism is uncommon and adrenal insufficiency usually occurs in a later stage and more slowly in adenomas when compared to other types, which can put these patients under life-threatening adrenal insufficiency when there is no diagnose [1].

Hyperprolactinemia may be related to stalk compression or to the immune-mediated destruction of lactotrophs [1], being difficult to evaluate its values in pregnant women or in postpartum [14]. Other possible symptoms to help diagnose are increase in body weight, around 18%, and temperature disruption (rare) [10].

Autoimmune hypophysitis follows an unknown clinical course, in which there have been reports of spontaneous resolution and recovery of pituitary function, as well as regression of pituitary growth in some cases [1,3].

In some situations, the LH natural course is unusually characterised by remission and recurrence [11]. In the present case, the patient's complaints started at 10 weeks of pregnancy, with improvement of the headaches without treatment, which only reoccurred one year postpartum. There is no specific serological or biochemical marker for LH and the diagnosis depends on the level of suspicion [7].

Diagnosis is confirmed by histopathological examination, which shows a diffuse lymphoplasmacytic infiltrate in which lymphoid follicles can be observed, as well as some plasma cells, eosinophils and fibroblasts. Fibrosis and atrophy of the pituitary gland may occur in later stages of the disease. [1]

Symptomatology varies depending on the gland's area affected and the degree of involvement [1,3]. There are no specific symptoms and its rarity might explain the relatively long-time lag before the diagnosis is made [4]. Clinical presentation and radiological findings may mimic a pituitary adenoma [7] and its differential diagnosis is difficult. There should be an increase in LH suspicion when there is an atypical development of hormonal deficiency, whether of ACTH and/or TSH with a normal GH and gonadotropin profile; symptoms occurring in a pregnant woman or postpartum and MRI imaging showing diffuse contrast enhancement with gadolinium [7].

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The laboratory evaluation consists in evaluating the adrenal and thyroid function, prolactin, IGF 1, FSH, LH, testosterone [men] and estradiol [women], electrolytes, fasting glucose, plasma and urine osmolality, antidiuretic hormone if there is suspicion of diabetes insipidus [2]. Routine blood tests, C-reactive protein, sedimentation rate [2]. Thyroid antibodies, pituitary antibodies, anti-Ro, anti-La, anti-SSa, anti-Ds-DNA, if concomitant autoimmune features are present [2]. In order to exclude sarcoidosis, ACE and soluble IL-2 receptor assessment
in serum was performed in some centres [10]. Thorax x-ray and interferon assay if history of travel and tuberculosis is suspected [2]. The patient should also do a magnetic resonance imaging and an ophthalmological assessment, including visual fields.

It is frequent to associate with other endocrine and non-endocrine autoimmune diseases [11] and the presence of organ-specific antibodies in patients with LH is another argument to support the autoimmune involvement in this disease [11].

This is also supported by the positive response to immunosuppressive therapy and the manifestation of remission and recurrence cycles which occur in the natural history of the disease, similar to those described in other autoimmune diseases [11]. In this case, the complaints started at 10 weeks of pregnancy, with recurrence 1 year postpartum.

The most common association is with Hashimoto’s thyroiditis and Graves’ disease [11].

There are several methods to detect anti-pituitary antibodies [ELISA, radio-ligand assay, immunoblotting and immunofluorescence] and the prevalence of antibody-positive hypophysitis is 11-73% depending on the antigen[s] tested and the technique used [1]. However, the pathogenic role of these auto-antibodies is unclear and they are not specific to hypophysitis [1]. In the case, described above, the antibodies assay was negative.

Other situations may be detected, such as Cushing’s syndrome, other adenomas, empty sella syndrome, Sheehan’s syndrome and autoimmune diseases [3].

The Gadolinium-enhanced pituitary MRI is the preferred radiological test and hypophysitis should be suspected when there is a symmetrical and homogeneous enlargement of the gland, and stalk thickening without deviation. The sellar floor is rarely involved and there is a diffuse and homogeneous enhancement after gadolinium injection [2]. Central hypopituitarism suggests necrosis or cyst formation and has been reported in 32% of cases from a study in Germany [10] and our radiological image showed similar findings. In a more advanced stage of the disease, pituitary atrophy may occur resulting in empty sella [1]. Although some features may differ between adenoma and LH, imaging may be atypical and about 40 to 50% of pre-surgery cases are diagnosed as adenomas [1,7].

Treatment for this disease is controversial given its rarity, variable natural history and, in some cases, there is spontaneous remission without any treatment [1,7,10]. Caturegli et al. reported that only 4% of patients had spontaneous remission with recovery of pituitary function, while most patients will require long-term replacement of one or more pituitary axes [1,5].

The treatment includes reducing the size of the pituitary mass and/or replacing the defective endocrine function.

In the absence of severe compression symptoms, a careful follow-up is strictly required in patients without symptomatic extracranial expansion or adrenal insufficiency [11].

A death rate of 7% has been described in several cases of patients with primary hypophysitis and is probably related to unrecognised acute adrenal insufficiency [11]. If there are pituitary deficits, it is necessary to replace it in physiological doses, carefully monitoring for adrenal insufficiency and avoid causing it with thyroxine replacement therapy in case of parhypopituitarism.

Glucocorticoids are an effective treatment of LH, in which they reduce the size of the mass and are used after as a replacement therapy for significant adrenal insufficiency [11]. Glucocorticoids remain the cornerstone of medical treatment [2] and its use as a front-line measure seems reasonable due to its lymphocytolytic properties [5]. The most commonly used glucocorticoids have been prednisone [from 20 to 60 mg/day], hydrocortisone [20 mg/day], and methylprednisolone [120 mg/day for 2 weeks] [5]. The use of prednisone 10 mg/day was effective in reducing the pituitary growth in 62.5% of the cases [3]. Dose and requirement of glucocorticoids vary with disease stage, and it is likely that fibrous stages of autoimmune hypophysitis [AH] will be unresponsive to glucocorticoids [5]. Honegger et al. documented excellent initial responses to high-dose glucocorticoids, with radiological improvement, stability and progression in 65%, 31% and 4% of cases, respectively [10,15], despite the risks of its side-effects. Recurrence may occur after its suspension, but also within a normal progressive withdrawal [10]. Hormone deficiencies improved with glucocorticoids only in 15% of patients, while they remained stable or worsened in 70% and 15% of cases, respectively [15]. The positive effect of hormonal replacement was no longer observed in some cases after its suspension; however, this was not the case for neurological symptoms [14,15]. The presence of central diabetes insipidus appears to be an unfavourable prognostic factor for response to glucocorticoids [1].

Other authors suggest immunosuppressive agents such as azathioprine, methotrexate or cyclosporin A when there is no response, there is resistance or when the patient develops adverse effects to glucocorticoids [1,3,10]. Azathioprine is the most commonly used immunosuppressive agent at present, while in the coming years, it is likely we will see more focused monoclonal antibody-directed therapy such as rituximab [2].

Most reported patients responded to immunosuppressive treatment and remained recurrence-free [10] but, the total number of treated patients is still low [10]. Although the experiment is limited, its results are promising [10]. The long-term effects are unclear [1] and there is a need for controlled studies to inform practice. The benefit of dopamine agonists in the evolution of LH is unproven, but it can be useful in cases where there is hyperprolactinemia [11].

In recent reports, there has been a decline in surgery approaches, given the positive results with steroid therapy [2]. Surgery is a viable option for those patients with serious and progressive damages that cause visual field, visual acuity or ocular movements because these lesions can cause permanent or temporary complications, such as haemorrhage, cerebrospinal fluid leaks and diabetes insipidus [11]. It may be necessary in cases that are not responsive to corticotherapy, and leads to a definitive diagnosis regardless of the inherent risks.
In the clinical case presented here, the patient underwent surgery because there were ocular complaints and a radiological suspicion of an optic chiasm lesion, which resulted in the diagnosis of lymphocytic hypophysitis.

The rate of recurrence of the lesion after surgery was reported to be 11—25% [1]. Recurrences were observed 0.7 years following surgery [10]. However, Honegger et al. observed progression/relapse of the disease in 25% of patients after a mean follow-up of 3 years [15]. Relapse represents the natural course of hypophysitis rather than being the result of insufficient surgical resection [10].

Stereotactic radiotherapy has been used in selected cases that were not responsive to medical or surgical therapy, or with recurrences [1,11], however, more studies need to be carried out. Its role remains uncertain and should be considered as a last resort [10].

There is a significant delay between onset of symptoms and LH diagnosis [4]. Although there is reasonable morbidity associated to LH, its prognosis is good [4] and depends on the inflammatory infiltrate degree, duration, residual fibrosis and response to treatment [3]. No prospective control studies have examined the treatment of hypophysitis and a limited number of case details the natural history of untreated disease [16].

After treatment, the timing and follow-up vary from case to case. To date, there are few studies with published guidelines for the follow-up of patients with LH in spontaneous remission, medical or surgical treatment.

Patients in which there was spontaneous resolution of the LH need active monitoring, through endocrinological examinations, usually every six months, annual imaging and, if necessary and according to the specialist professional opinion, ophthalmology evaluation. If there is no progression, these timings can be extended to a periodicity of 2 years. This procedure of follow-up is the usual used for pituitary lesions [8].

In patients whom it was necessary medical or surgical therapy, a specific program is needed to assess pituitary function and local invasion, through imaging and visual examination. Sumida et al. in a study involving 11 patients [6 with adenohypophysitis and 5 with neurohypophysitis] found that in adenohypophysitis patients, enlargement of the pituitary was found in all of them on initial image and continued from 1 to 17 months. Enlargement of the stalk was found in five patients on initial image and continued from 3 to 17 months. In two patients, recurrence was seen at 52 and 3 months. In neurohypophysitis, diabetes insipidus disappeared in only one patient at 14 months. However, loss of high intensity of the posterior lobe was found in all patients and continued on all follow-up images. Enlargement of the stalk was found in all patients on initial image and continued more than 12 months. Enlargement of the pituitary was not found in any patients on initial image, and atrophy of the pituitary was seen in three on follow-up image. Recurrences were not found during follow-up period of the study [17].

The authors suggest, given the procedure for hypophysitis monitorization, that the follow-up for LH must include hormonal evaluation, every 6 months, ophthalmology evaluation, with frequency established by the specialist according to the case, and periodic imaging study, at least once a year, during the first 3–4 years and then the frequency will depend on the course of the disease [8].

Some patients require permanent replacement treatment, which must be carefully monitored by pituitary hormonal assays every 6 months [8]. In case of clinical, analytical and/or imaging changes, these periods can be shortened.

Multidisciplinary teams are essential for the approach of LH cases and these teams should include specialists from endocrinology, ophthalmology, imaging and neurosurgery [17].

**Conclusion**

The only diagnose of LH is histopathological but a high degree of suspicion with clinical, laboratory and radiological findings can lead to a medical and effective treatment, avoiding surgery. Glucocorticoids therapy is the cornerstone of medical treatment. Surgery can help with the differential diagnosis and the relief of compression symptoms. Multidisciplinary teams are essential for the approach of LH cases.

**References**


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