CASE REPORT

JIACM 2019; 20(3-4): 220-23

Steroid-Responsive Neuroimaging Resolution in Lymphocytic Infundibulo-Neurohypophysitis

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Abstract

Though lymphocytic infundibulo-neurohypophysitis (LINH) is an uncommon cause of central diabetes insipidus, it should be strongly considered in a case of central diabetes insipidus whose neuroimaging shows thickening of pituitary stalk more than 4 mm. It is characterised by lymphocytic infiltration of the posterior pituitary gland and pituitary stalk (infundibulum). The patient typically presents with polyuria and polydipsia. In most cases, detailed clinical history and neuroimaging can point towards LINH. Rather, the definitive diagnosis of LINH can only be made on a pituitary biopsy, but this procedure is hardly indicated in patients without mass effect as there are chances of further deterioration of pituitary function. Also, there are adverse events associated with an invasive procedure. It is thought to be of autoimmune origin and steroids are given along with vasopressin to manage this central diabetes insipidus.

Introduction

Hypophysitis can be classified histologically into various types like lymphocytic, granulomatous, xanthogranulomatous, xanthomatous and necrotising hypophysitis, besides causes secondary to systemic inflammation like sarcoidosis, histiocytosis, xanthoma disseminatum, granulomatosis with polyangitis (Wegener's), infections, or from localised pituitary/sellar masses. Out of these, lymphocytic hypophysitis is a rare disorder of autoimmune aetiology in which the pituitary gland is infiltrated with T-lymphocytes. It has a prevalence of around 5 per million and represents approximately 0·5% of cases of hypopituitarism, less than 1% of pituitary masses and 2% of non-functioning pituitary lesions. It more commonly occurs in females. Depending upon the location of the lesion, there are two forms; first, lymphocytic adenohypophysitis (LAH) which is commoner among the two and has been described more frequently during pregnancy and in the early post-partum period. This presents with enlarged anterior pituitary gland with usually multiple hormonal deficiencies. The second is lymphocytic infundibulo-neurohypophysitis (LINH) which predominantly affects the pituitary stalk along with the posterior lobe of the pituitary gland[1]. We report a case of a 22-year-old male who presented with symptoms of diabetes insipidus of central origin. Further investigations revealed lymphocytic infundibulo-neurohypophysitis to be the cause of central diabetes insipidus and there was dramatic response to steroid therapy.

Case presentation

A 22-year-old male presented in our hospital with a history of polyuria and polydipsia for three months. He reported urine output in excess of 6 litres. There was no past history of head trauma, chronic illness like tuberculosis, asthma, epilepsy, or any drug intake. Also, there was no significant family history.

On examination, pulse rate was 76/minute and blood pressure 118/76 mmHg. Body temperature was 36.8° C. His height was 168 cm and weight 58 kg; BMI being 20.54 kg/m^2. There was no pallor, cyanosis, clubbing, pedal oedema or lymphadenopathy. Examination of the cardiovascular, respiratory, abdominal and nervous system was unremarkable.

Investigations

Complete haemogram was normal. His plasma glucose was 97 mg/dl, blood urea 34 mg/dl, serum Na^+ 140 mEq/l, serum k^+ 3.8 mEq/l, serum Cl^- 108 mEq/l. Serum osmolality was 291 mosm/kg H_2O. 24 hours urinary volume was 6.5 litres and urinary osmolarity was 58 mosm/l during *ad libitum* fluid intake. Urine specific gravity was 1.005. Arterial blood gas analysis revealed pH 7.38 and HCO_3^- 22.3 mmol/l. Renal function and liver function tests were within normal limit. HIV test was nonreactive. Tuberculin test and thyroid function tests were normal. Plasma angiotensin-converting enzyme level was normal. All anterior pituitary hormones (serum prolactin, growth hormone, LH, FSH) were within

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normal limits. ANCA and IgG4 levels were in normal range. The cerebrospinal fluid analysis did not reveal any evidence of infection or malignancy. Visual field testing was normal.

Water deprivation test: He was put on water deprivation with monitoring of urine output, serum and urine osmolality. When there was a reduction in body weight by 3%, nasal desmopressin 10 µg was given. Urine osmolality doubled 2-hours after desmopressin dose which established diagnosis of central diabetes insipidus.

Imaging: Chest X-ray PA view and ultrasound abdomen were normal. T_1-weighted images of MRI pituitary showed thickening (5 mm) of pituitary stalk and infundibulum (Fig.1 and 2). There is also loss of posterior pituitary "bright spot" on T_1-weighted images (Fig. 3).

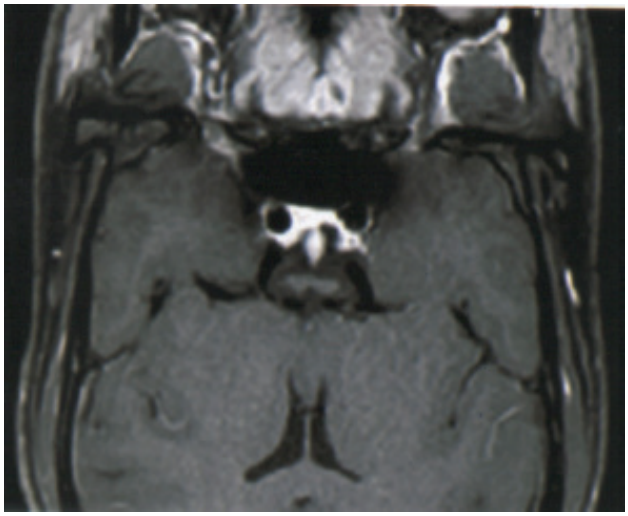

Fig. 1: *Contrast-enhanced magnetic resonance T1-weighted image, coronal section demonstrates contrast enhancement of thickened infundibulum.*

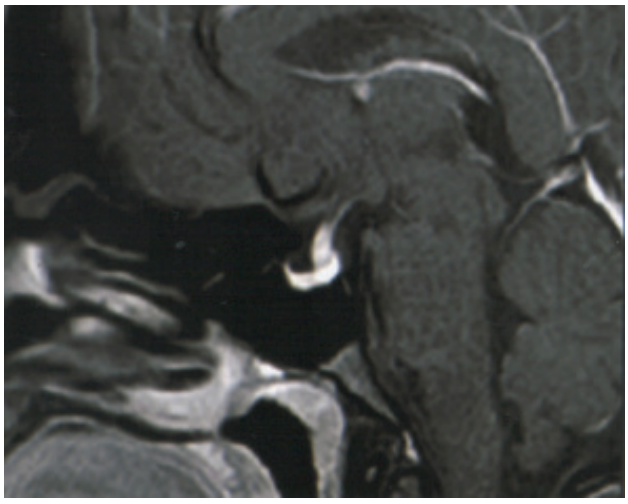

Fig. 2*: Contrast-enhanced magnetic resonance T1-weighted image, sagittal section shows contrast enhancement of thickened infundibulum.*

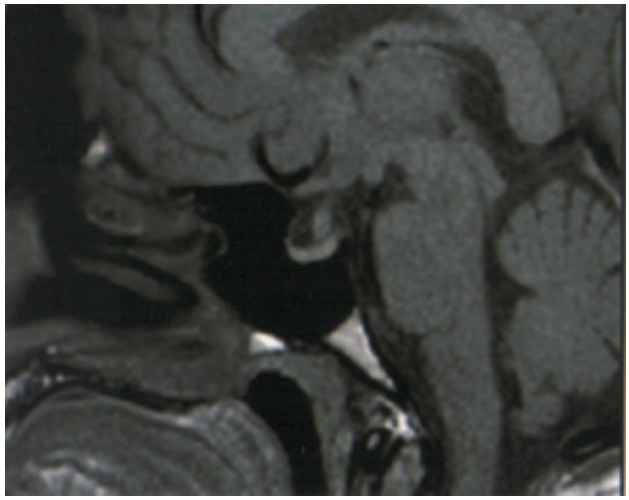

Fig. 3: *Magnetic resonance T1-weighted image, sagittal section shows thickened infundibulum with loss of posterior pituitary hyperintensity.*

Differential diagnosis

Central diabetes insipidus: causes include:-

- Infiltrative-sarcoidosis, haemochromatosis, histiocytosis X.
- Granulomatous hypophysitis
- Parasellar mass- germinoma, ependymoma.

Treatment

He was diagnosed as a case of central diabetes insipidus due to lymphocytic infundibulo-neurohypophysitis. Treatment with tablet prednisolone (1 mg/kg/day) once a day and nasal spray desmopressin (10 µg/dose) twice a day was started and continued for two weeks. Urine volume normalised and he was relieved of the symptom of polyuria and polydipsia. Desmopressin (10 µg/dose) was tapered to once a day after two weeks and stopped after 8 weeks. The dose of prednisolone was gradually tapered by 10 mg/week, total duration being 8 weeks.

Outcome and follow-up

After four months of follow-up, he is doing well without desmopressin. MRI pituitary revealed resolution of infundibular thickening and presence of posterior pituitary bright spot.

Discussion

Lymphocytic infundibulo-neurohypophysitis (LINH) was first reported by Imura and colleagues way back in 1993[1]. A patient with LINH typically presents with osmotic symptoms of polyuria and polydipsia associated with

central diabetes insipidus.

The pathogenesis involves mechanistic infiltration of the posterior pituitary gland with lymphocytes, mainly T-lymphocytes, which results in the destruction of the normal architecture. Histological findings typically reveal a polyclonal inflammatory infiltrate with a mixed T- and B-cell population, and in addition, diffuse infiltration of mainly mature lymphocytes (T-lymphocytes, CD4 positive cells predominantly) and some plasma cells are usually demonstrated[2]. Dysfunction of endocrine cells and impairment of vasopressin release along with the loss of normal tissue and concomitant atrophy are likely explanation for the majority of LINH patients having near-permanent diabetes insipidus, requiring replacement therapy for a quite long period. The aetiology includes granulomatous diseases like sarcoidosis, histiocytosis, xanthoma disseminatum, granulomatosis with polyangitis (Wegener's), necrotising, immunoglobulin G4 (IgG4)-related systemic disease (IgG4-RD), and chemotherapy agents including Ipilimumab, tremelimumab[3]. It can be associated with other autoimmune conditions including Hashimoto's thyroiditis, Graves' disease, systemic lupus erythematosus, and Behcet's disease.

Diagnostic role of pituitary antibodies in LINH is not well understood. Some antibodies that have been tested so far include anti-growth hormone (anti-GH), anti α-enolase, arginine vasopressin antibodies (AVP Ab). There have been conflicting results from previously tested pituitary antibodies most likely reflecting the different methodologies used. Out of these, anti-growth hormone (anti-GH) and anti α-enolase have been studied specifically for LINH but no significant diagnostic accuracy could be ascertained. De Bellis *et al*, studied the presence of AVP antibodies in patients with central diabetes insipidus and showing thickening of pituitary stalk consistent with LINH. The study revealed that AVP antibodies were consistently found in patients of central diabetes insipidus with pituitary stalk thickening, while patients without pituitary stalk thickening did not have AVP antibodies. Therefore, the presence of AVP antibodies appears to be a good marker of autoimmune central diabetes insipidus in patients with LINH[4]. Later, Pivonello *et al*, demonstrated that the presence of AVP Ab was significantly and independently associated with autoimmune diseases and pituitary stalk thickening[5]. So, when AVP Ab is coupled with clinical and neuroimaging findings, it is helpful in ascertaining the diagnosis of LINH.

Water deprivation test is an essential part of work-up for characterisation of diabetes insipidus, though it is not needed in patients who present with serum hyperosmolarity at baseline. Change in urine osmolality after desmopressin nasal spray helps to differentiate between partial central diabetes insipidus, partial nephrogenic diabetes insipidus and primary polydipsia.

Measurement of plasma arginine vasopressin can also differentiate between central and nephrogenic diabetes insipidus, but there are technical difficulties in laboratory measurements. One is its very short half-life which makes it difficult to quantify, second is lack of standardisation of quantifying methodologies. To overcome this difficulty, plasma copeptin is postulated as a surrogate marker of AVP release. Copeptin is the c-terminal portion of the arginine vasopressin (AVP) precursor and is co-secreted with AVP and neurophysin II from the neurohypophysis. It has a longer half-life and is easier to measure than AVP. Normal plasma value ranges from 1 to 12 pmol/l, slightly higher in men than in women. It has been suggested as an additional diagnostic tool during the water deprivation test in the polyuria-polydipsia syndrome[6]. Our patient was not subjected to this test as there were typical neuroimaging findings in our patient and there was no confusion in diagnosis.

Recently, Iwama *et al*, studied various autoantigens in LINH and found that rabphilin-3A was most diagnostically useful autoantigen. This antigen is expressed in posterior pituitary and hypothalamic vasopressin neurons and not in the anterior pituitary. Antibodies to rabphilin-3A may serve as a biomarker for diagnosis of LINH[7]. This test is still not available commercially and so was not applied in our case.

Imura *et al*, conducted MRI pituitary on 17 patients presenting with idiopathic diabetes insipidus. All patients lacked the hyperintense signal ("bright spot") of the neurohypophysis that is present in normal subjects. But thickening of pituitary infundibulum/stalk and/or enlarged neurohypophysis was present only in 9 out of 17 patients[1]. On imaging, thickening of the stalk usually have the tumour-like appearance, and there might be difficulty in differentiating it from a pituitary tumour. Our patient had typical findings on MRI pituitary.

Although, the gold standard for definitive diagnosis of LINH is the histological examination of pituitary biopsy through a transnasal-transsphenoidal approach. But it is an invasive procedure with the significant risk of deterioration of pituitary functions. So, it is rarely needed for diagnostic evaluation of LINH as other laboratory markers and neuroimaging is sufficient to make a diagnosis. It may be considered in the setting when the clinical diagnosis is in doubt.

Most patients with LINH require long-term desmopressin (DDAVP) therapy. Though there have been no randomised controlled trials for use of steroids as first-line treatment, it has been seen that glucocorticoid use is associated with disease regression in some cases. Our case responded well to steroids and there were no adverse effects. It makes our

case a rare presentation of steroid-responsive LINH. Previously, steroids have been used in few LINH cases and regression of thickened pituitary stalk has been seen[8].

Pituitary surgery is not generally needed in LINH as the pituitary stalk thickening hardly causes any mass effect. However, few patients who present with mass effect in the form of vision loss or cranial nerve involvement, surgical decompression can be undertaken only if the response to glucocorticoid therapy is not rapid enough[9]. It is also recommended that surveillance for lymphoma and other diseases should be done meticulously while the patient is on steroids.

Long-term follow-up of these patients should be done and serial neuroimaging is mandatory to demonstrate a reduction in the size of pituitary stalk thickening over time as well as routine hormonal and biochemical assessment.

Our case presented a scenario with excellent response to steroids and this was accompanied by neuroimaging resolution too. So, it can be concluded that timely institution of steroids not only halts disease progression but also can eliminate disease altogether.

Learning points/take home messages

- Determining whether diabetes insipidus is central or nephrogenic is of primary importance.
- A systematic approach is required in determining the cause of diabetes insipidus.
- LINH can be diagnosed on neuroimaging and pituitary biopsy is rarely needed.
- Steroid use in LINH is associated with faster recovery.

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