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Case Report

Lymphocytic/autoimmune hypophysitis - A rare case of hypopituitarism presenting with dizziness and lethargy in a sixty year old male

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Introduction

Hypopituitarism occurs due to decreased hormone secretion from the pituitary gland secondary to a disorder of the hypothalamus or the pituitary. Hypophysitis is inflammation of the pituitary gland, with lymphocytic hypophysitis being the commonest cause [1]. This rare condition is characterised by initial lymphocytic infiltration followed by destruction of the gland [2]. It is predominantly a disease of young females occurring during the postpartum period [3]. Males are affected at an older age [1]. The anterior pituitary is commonly involved and is called lymphocytic adenohypophysitis. Historically, it was hypothesized that only the anterior pituitary is involved in this condition. Increasing awareness and recognition has led to the identification of patients presenting with posterior pituitary involvement (lymphocytic infundibulo hypophysitis) or involvement of both (lymphocytic panhypophysitis) [4].

Case Presentation

A sixty-year-old male presented with a six-month history of increasing dizziness and lethargy. He also had several fainting episodes which were postural in nature. They occurred at any time of the day and were unrelated to meals. The fainting episodes were not associated with chest pain, palpitations, vertigo or hearing loss. He had never had fits. He has had several admissions to the local hospital where he was given symptomatic treatment with intravenous fluids. He complained of cold intolerance, dryness of skin and malaise. He also had loss of body hair and erectile dysfunction for the previous 5 months. He denied polyuria or polydipsia. His illness restricted his daily activities, and he could not cope up with his job as a security officer.

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One year back, patient had developed a gradual onset, severe, persistent headache which was not associated with any visual impairment or above symptoms. Due to an elevated erythrocyte sedimentation rate (ESR) and older age he was suspected of having giant cell arteritis (GCA) and started on high dose prednisolone (60 mg) daily with resolution of his headache. As temporal artery biopsy had not revealed any evidence of granulomatous inflammation, prednisolone was tailed off.

He did not have any long standing illness. He consumed half a bottle of alcohol per week and was a smoker with a five pack-year history. He had given up both habits due to recent ill health. He was a married man who had fathered two children. He was pale with a body mass index of 20kg/m^2. He had dry, coarse skin without a goitre. Sparse pubic and axillary hair with testicular atrophy was noted. His cardiovascular system examination revealed a significant blood pressure postural drop with a postural tachycardia and a low volume pulse. His visual fields and the rest of the examination was normal. His capillary blood sugar (CBS) values were low during repeated assessments. Initial resuscitation with intravenous fluids and intravenous dextrose was done with frequent monitoring of CBS.

His basic investigations revealed a moderate normochromic normocytic anaemia with a high erythrocyte sedimentation rate (ESR) (Table 1).

Table 1: Basic blood investigations

Investigations	**Results (Normal Range)**
FBC	
WBC	6× 10^3/µL(4- 11 × 10^3 /µL)
N	64% (40- 60 %)
L	23%(20- 40%)
E	0.3% (1-4 %)
Hb	10 g/dl(13.5- 17.5g/dL)
Plt	241× 10^9/ µL (150- 450 × 10^9/µL)
CRP	8 mg/L(<5 mg/L)
ESR	60 mm/1st hour(<20/ 1st hour)
Blood picture	Normocytic, normochromic anaemia of chronic disease
AST	32 U/L(5- 40 U/L)
ALT	40 U/L(7- 56 U/L)
ALP	98 U/L(40- 129 U/L)
Gamma GT	25 U/L(8- 61 U/L)

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Total protein	6.8 g/dL(6- 8.3 g/dL)
Globulin	3.3 g/dL(2- 3.5 g/dL)
Albumin	3.5 g/dL(3.4- 5.4 g/dL)
S. Cr	0.8 mg/dL(0.74- 1.35 mg/dL)
SE	
Na^+	138 mmol/L(135- 145 mmol/L)
K^+	4.5 mmol/L(3.5- 5 mmol/L)
Ca^+	2.4 mmol/L(2.2- 2.6 mmol/L)
PO_4^{3-}	1.3 mmol/L(1.12- 1.45 mmol/L)
Mg	0.9 mmol/L(0.85- 1.1 mmol/L)

FBC, full blood count; WBC, white cell count; N, neutrophils; L, lymphocytes; E, eosinophils; Hb, haemoglobin; Plt, platelets; ESR, erythrocyte sedimentation rate; CRP, c- reactive protein, AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; Prot, protein; Glb, globulin; Alb, albumin; S.cr, serum creatinine; SE, serum lectrolytes; Na, sodium; K, potassium; Ca, calcium; PO_4^{3-}, phosphate; Mg, magnesium;

His hormonal profile (Table 2) revealed evidence of hypopituitarism. Patient had secondary hypoadrenalism, secondary hypogonadism and secondary hypothyroidism.

Table 2: Hormonal profile

Investigations	**Results (Normal range)**
9 am cortisol	80 nmol/L (140- 690 nmol/L)
Short synacthan test Post stimulation 1 hour	103 nmol/L (> 550 nmol/L)
ACTH	1.8 pmol/L (2.2- 13.3 pmol/L)
PTH	40 pg/mL (10- 55 pg/mL)
Prolactin	80 nmol/L (118- 618 nmol/L)
TSH	1.17 mIU/L (0.5- 5 mIU / L)
Free Thyroxine	0.46 ng/dL (0.9- 2.3 ng/dL)
FSH	0.46 IU/L (1.42- 15.4 IU/L)
LH	0.07 IU/L (1.42- 15.4 IU/L0
Testosterone	70 ng/dL (280- 1100 ng/dL)

ACTH, adrenocorticotropic hormone; PTH, parathyroid hormone, TSH, thyroid stimulating hormone; FSH, follicular stimulating hormone; LH, luteinising hormone

Non-contrast computed tomography of head was normal. Magnetic resonance imaging of brain with pituitary protocol revealed an appearance of a microadenoma (5×5mm) with delayed contrast enhancement (Figure 1).) (Fig 1). It was inconsistent with the hormonal

profile as microadenomas are usually non-functional tumours without a mass effect or functional hormone secreting tumours. There was no infundibular thickening which is usually seen early in infiltrative diseases such as sarcoidosis and hemochromatosis.

Patient had a positive antinuclear antibody (ANA) test but there were no clinical features suggestive of autoimmune connective tissue disorders. He was negative for anti-ds-DNA and anti-Smith antibodies and his complement three and four levels were normal. He was negative for serum anti- neutrophil antibody (ANCA).
He did not have a past or close contact history of tuberculosis and denied any chronic cough. His chest X-ray and high-resolution computed tomography (HRCT) of chest did not reveal any evidence of tuberculosis or sarcoidosis (Table 3).

Table 3: Imaging and other investigations

Investigations	**Results**
Mantoux (mm)	<5
CXR- PA	No inflammatory shadows or hilar adenopathy
USS abdomen and pelvis	No adrenal masses.
NCCT brain	Normal
MRI brain with pituitary protocol	Lesion in the right side of anterior pituitary 5×5 mm size. Stalk appear normal. Pituitary micro adenoma.
HRCT chest	No evidence of sarcoidosis or tuberculosis
ECG	Normal sinus rhythm
2D echocardiography	Normal cardiac chambers. EF- 60% No pericardial collections.

CXR-PA- chest x ray- posteroanterior; USS, ultrasound; NCCT, non-contrast computed tomography; MRI, magnetic resonance imaging; HRCT, high resolution computed tomography; ECG, electrocardiography; 2D, 2- dimensional.

His cerebrospinal fluid analysis was normal. His serum angiotensin converting enzyme (ACE) levels were normal with a normal iron profile and serum IgG 4 level (Table 4).

Table 4: Advanced blood investigations

Investigations	**Results (Normal range)**
Serum osmolality	283 mosm/kgH_2O(275- 295 mosm/kgH_2O)
Urine osmolality ()	430 mosm/kg H_2O(50- 1000 mosm/kgH_2O)
ANA ab	1:1000
Anti- dsDNA ab	Negative
Anti- Smith ab	Negative

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C3 level ()	102 mg/dL(80- 178 mg/dL)
C4 level ()	34 mg/dL(12- 42 mg/dL)
p- ANCA	Negative
c- ANCA	Negative
Serum IgG4 level	50 mg/dL(10- 140 mg/dL)
SPEP	Normal range
Serum ACE	15 U/L(14- 82 U/L)
Serum ferritin	300 ng/mL(20- 250)
Transferrin saturation	20%(20- 50%)
Serum iron	96 µg/dL(60- 170 µg/dL)
PSA	1.5 ng/mL(<4.5 ng/mL)

ANA, anti- nuclear; ab, antibodies; ds-DNA, double strandard deoxyribonucleic acid; c3, complement factor 3; c4, complement factor 4; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; c- ANCA, cytoplasmic anti-neutrophil antibodies; IgG4, immunoglobulin 4; SPEP, serum protein electrophoresis; ACE, angiotensin converting enzyme; PSA, prostate specific antigen

A multidisciplinary approach with endocrinology expertise was taken. The history of severe headache, out of proportion to the small pituitary mass, initial rapid response of headache to corticosteroid treatment one year back, appearance of features of hypopituitarism after resolution of the headache, clinical findings of hypopituitarism despite MRI findings of a microadenoma, no infundibular thickening in the MRI, involvement of the anterior pituitary only (infiltrative lesions would cause an early cranial diabetes insipidus), negative screening for other common infiltrative causes of hypopituitarism, a high ESR and a positive ANA titre, all supported the final diagnosis of lymphocytic / autoimmune hypophysitis.

The patient was started on corticosteroid treatment followed by thyroxine replacement to prevent precipitation of an adrenal crisis. Three times daily dose of hydrocortisone 10mg, 5mg, 5mg and thyroxine 50µg/day was started. The patient was also started on intramuscular (I.M.) testosterone 250µg/weekly dose as he did not have any features of bladder outflow obstruction or evidence of prostatomegaly in ultrasound scan.

Upon initiation of corticosteroids the patient improved dramatically with resolution of dizziness and fainting episodes. His CBS values returned to normal. He was feeling energetic and was able to gradually resume day to day routine activities. Patient and family `were advised on the importance of compliance with medications, especially corticosteroids. He was issued a steroid card with advice to double the steroid dose in case of any intercurrent illness or other stressful condition. Upon discharge, follow up was arranged at both endocrine and medical clinics.

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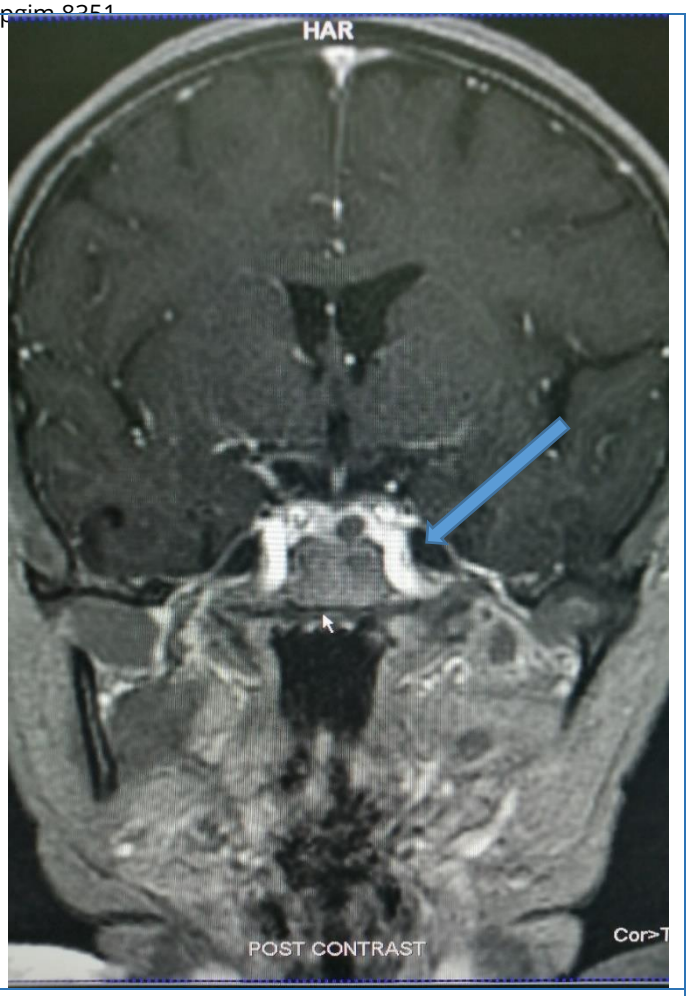

Figure 1: MRI scan of pituitary revealed a mass of 5×5mm in size with delayed contrast enhancement

Discussion

Lymphocytic hypophysitis (LH) is a rare form of chronic inflammation which affects the pituitary gland [1]. Other less frequent causes of hypophysitis include granulomatous, plasmacytic and xanthomatous disease. Its estimated incidence is one per nine million per year [5]. Growing awareness of this condition among physicians, frequent use of imaging and high rates of transphenoidal surgery may have contributed towards a recent increase in incidence and prevalence of this condition. The association with pregnancy and the postpartum period, lymphocytic infiltration of the gland [6], coexistence with other autoimmune diseases such as Hashimoto's thyroiditis, systemic lupus erythematosus [1] and the response to immunosuppressive drugs, all point towards an autoimmune component to the disease.

Affected individuals initially have a severe headache which is out of proportion to the size of pituitary lesion as was seen in this case. Anterior pituitary involvement is commonly seen. Preferential hypofunction of TSH and ACTH secreting cells has been described in the literature [3]. Patients presenting with hypogonadism is also increasingly reported [7]. All of the above typical clinical features were present in this patient. Diabetes insipidus secondary to posterior pituitary involvement occurs less frequently [8]. Some patients

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present with clinical features of both anterior and posterior pituitary involvement [9]. Hyperprolactenaemia due to stalk infiltration is also reported [6].

The gold standard for diagnosis of LH is histological examination of pituitary tissue which will demonstrate evidence of diffuse infiltration of the gland by lymphocytes [1]. But a non- invasive diagnosis by compatible clinical features, hormonal abnormalities and MRI findings is used in clinical practice [1]. MRI findings are usually of a pituitary mass mimicking an adenoma [10] as was seen in this patient. This can occur in up to about half of LH cases [11]. A strong, more homogenous enhancement of the anterior pituitary is more suggestive of LH [12]. Later in the disease, with immune destruction of the gland, it may appear as an empty sella syndrome on MRI [13].

Usually, a microadenoma is an incidental finding during a brain MRI where it is non-secretory or secretory in nature [14]. A pressure effect and destruction of secretory pituitary cells is not recognised. Even though the MRI revealed a microadenoma, the lack of evidence of hormonal hypersecretion helped us in arriving at our final diagnosis. On the other hand, infiltrative diseases such as sarcoidosis would show an early infundibular thickness on MRI [15]. They would also cause early diabetes insipidus during the disease course [16]. The diagnosis of LH is challenging, especially when it comes to differentiating it from more common non-functioning macroadenomas with pressure effects. A definitive diagnosis in these cases may be sought by histological examination of pituitary tissue. Anti-pituitary autoantibodies may be positive, but such tests are not yet widely available and their diagnostic utility is uncertain, especially when found in low titres [17]. They have low specificity and sensitivity [18].

Treatment for LH consists of replacement of deficient hormones, glucocorticoid treatment and surgical treatment [11]. Surgical management is favoured in cases of mass effect causing compression to secretory cells and surrounding structures. Additional benefit is the ability to get a tissue diagnosis. Current literature favours the non- surgical approach [19]. The need for repetitive surgery, sometimes, is the disadvantage of surgical management. Glucocorticoids act as anti-inflammatory agents as well as adrenal replacement therapy. Prednisolone, hydrocortisone or methylprednisolone are commonly used [20]. LH typically responds to glucocorticoid therapy with reduction in size of the mass and improvement of the hormonal profile [1]. Duration of treatment depends on the clinical response. Newer drug therapies with azathioprine [21] methotrexate [22] and rituximab [23] can be trialled for glucocorticoid unresponsive cases. Overall prognosis is good in LH [19]. Most cases regress overtime with adequate treatment.

Conclusion

LH is a rare but important cause of hypopituitarism. True incidence and prevalence may be underestimated due to lack of awareness of this clinical entity. It should be considered in the differential diagnosis of a hypo-functioning pituitary mass. It has a good prognosis if timely diagnosis and treatment is implemented to prevent the fatal complications of hypopituitarism.

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