Hypopituitarism due to Isolated Lymphocytic Hypothalamitis in a Young Girl

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ABSTRACT

Autoimmune hypothalamitis has been implicated in idiopathic central diabetes insipidus, and lymphocytic infiltration of hypothalamus has been reported in patients with lymphocytic hypophysitis manifesting as hypopituitarism with diabetes insipidus. Here, we report a case of young girl who presented with visual impairment, raised intracranial tension with hypopituitarism without diabetes insipidus, whose investigations revealed isolated lymphocytic hypothalamitis.

Keywords: Lymphocytic hypothalamitis, Hypopituitarism.

INTRODUCTION

Autoimmune hypothalamitis has been implicated in idiopathic central diabetes insipidus (DI) due to antibodies against vasopressin producing hypothalamic cells. Lymphocytic infiltration of hypothalamus has been reported in patients with lymphocytic hypophysitis (LH) manifesting as hypopituitarism with DI. A detailed search of literature did not yield any case of isolated lymphocytic hypothalamicis with hypopituitarism without DI. Here, we report a case of young girl who presented with visual impairment and raised intracranial tension with hypopituitarism without DI, whose investigations revealed isolated lymphocytic hypothalamitis.

CASE REPORT

An 18-year-old girl presented with dull aching global headache of 4 months duration, which began after a febrile illness which lasted 7 days. Few days after the onset of headache, she noticed gradual diminution of vision in both eyes. She was unable to see objects in her temporal fields. These symptoms were associated with nonprojectile vomiting, 3 to 4 episodes in a day. She had noticed progressive gait instability and subsequently required support to walk. There was no muscle weakness, involuntary movement, sensory symptoms or bladder and bowel involvement. Her parents had observed she had become very irritable and had altered sleep wake cycle. Four days prior to admission, there was deterioration in her sensorium and had poor comprehension. She had amenorrhea for one year. The patient had attained menarche at 13 years, but was amenorrheic for one year prior to her presentation with the present illness. There were no other symptoms of anterior or posterior pituitary dysfunction.

At admission, she had poor comprehension, was not oriented to time, place and person, was afebrile, pulse was 68 per minute, and blood pressure was 140/90 mm Hg. Pupils were mid-dilated and reacting sluggishly to light. Partial optic atrophy was seen in both the eyes. There was no papilledema or neck rigidity. She had all limbs moving. The deep tendon jerks were exaggerated and plantars were extensor. Rest of systemic examination was unremarkable. Noncontrast computerized tomography of brain showed a mass in suprasellar region. She was referred to endocrinology unit for evaluation. After collection of samples for biochemical and hormonal estimation, she was emergently treated with decongestive therapy. Her sensorium and orientation improved over next 3 days and she regained normal comprehension. She was able to walk with support, a day later. Blood pressure recorded now was 100/70 mm Hg without significant postural fall. Examination of eye at this stage showed a visual acuity of 1/60 in right eye and finger counting at one foot in left eye, bitemporal hemianopia, and partial optic atrophy in both eyes. She had no motor or sensory deficits. There were no signs of cerebellar dysfunction. She was pale, had sparse pubic and axillary hairs. Her urine output ranged from 1.2 to 2.0 liters per day.

Investigations revealed a hemoglobin of 11.2 gm/dL (14 ± 2.5), total leucocyte count 5,500/mm³ (4,000-11,000), platelets 1,87,000/mm³ (1,50,000-4,50,000), erythrocyte sedimentation rate 38 mm fall in first hour (0-20), fasting blood glucose 97 mg/dL (70-100), blood urea nitrogen 18 mg/dL (7-19), creatinine 0.8 mg/dL (0.5-1.6), sodium 140 mEq/L (135-149), potassium 4.1 mEq/L (3.5-5.0), SGOT 25 U/L (< 40), SGPT 28 U/L (< 40), alkaline phosphatase 154 U/L (< 250), calcium 8.6 mg/dL (8.5-10.5), phosphorous 3.8 mg/
Urine and cerebrospinal fluid examination were normal. Urine and blood cultures were sterile. Her urine spot sodium was 26 mEq. Water deprivation test was not done in view of her condition and normal urine and plasma osmolality. She had normal chest radiograph. Free T3 measured 3.33 pg/mL (2.4-4.2), free T4 0.97 ng/mL (0.8-1.7), thyroid stimulating hormone 1.11 μIU/mL (0.5-6.5), luteinizing hormone 0.01 IU/L (0.5-15), follicle stimulating hormone 0.01 IU/L (0.2-10), estradiol 17.6 pg/mL (60-200), prolactin 46.9 ng/mL (< 25) and random serum cortisol 4.3 μg/dL. Magnetic resonance imaging (MRI) of brain (Figs 1 to 3) showed a well-defined, lobulated suprasellar mass in the area of hypothalamus, which appeared homogenously hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images with predominant cystic areas within and had perilesional edema. The lesion measured 2.5 cm (anteroposterior) × 3.2 cm (craniocaudal) × 2.8 cm (transverse) in dimensions. Superiorly, the lesion was indenting the body of lateral ventricles, inferiorly the optic chiasma was encased and laterally it infiltrated anterior thalami bilaterally. There was no extension into the sella. The pituitary and stalk were distinctly made out separately with preserved bright spot.

Differential diagnoses of hypothalamic opticochiasmatic glioma, craniopharyngioma, sarcoidosis, suprasellar germinoma were considered. Alpha fetoprotein was 0.55 ng/ml (< 3), beta human chorionic gonadotropin 0.02 IU/L (< 5 IU/L), serum angiotensin converting enzyme 30.0 U/L (8.0-65.0). She underwent transcranial excision of tumor. Postoperative period was uneventful. Histopathological examination of the tissue showed focal dense lymphocytic infiltrate with perivascular lymphocytic cuffing, sheets of foamy macrophages interspersed with glial cells (Fig. 4). There were no neutrophils, giant cells, granulomas, caseous necrosis, neoplastic cells or Rathke’s

**Fig. 1:** Preoperative magnetic resonant imaging: T1-weighted post contrast sagittal images of sella and parasellar region showing a suprasellar mass with its epicenter at hypothalamus, hypointense to the brain parenchyma with areas of necrosis and ring like enhancement. The pituitary is seen separately from the lesion and posterior pituitary bright spot is maintained

**Fig. 2:** Preoperative magnetic resonant imaging: T1-weighted post contrast coronal images of sella and parasellar region showing a suprasellar mass with extension into lateral ventricles

**Fig. 3:** Preoperative magnetic resonant imaging: T2-weighted coronal images of sella and parasellar region showing hyperintense suprasellar mass with perilesional edema

**Fig. 4:** Histopathological examination hematoxylin and eosin staining, 40X magnification, showing dense lymphocytic infiltrate predominantly perivascular in location in a background of glial tissue
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pouch remnants. Zeil-Neilson staining was negative for acid fast bacilli. Immunohistochemistry staining was positive for CD 20 (Fig. 5; 70%, B lymphocytes), CD3 (Fig. 6; 30%, T lymphocytes) and CD 68 (Fig. 7; histiocytes).

Postoperatively, her field of vision improved and visual acuity improved to 6/36 in right eye; however, vision remained unchanged in left eye. Free T3 measured 2.06 pg/mL (2.4-4.2), free T4 0.70 ng/mL (0.8-1.7), thyroid stimulating hormone 0.09 μIU/mL (0.5-6.5), luteinizing hormone 0.01 IU/L (0.5-15), follicle stimulating hormone 0.27 (0.2-10) IU/L, prolactin 54.9 ng/mL (< 25), basal cortisol 2.4 μg/dL (5.0-24.0), post ACTH cortisol 4.5 μg/dL (>18), peak growth hormone response to clonidine stimulation test 0.22 ng/mL (> 5). Postoperative MRI showed a reduction in the size of the lesion—1.57 cm (anteroposterior) × 1.08 cm (craniocaudal) × 1.68 cm (transverse). The pituitary was normal with preserved bright spot, pituitary stalk and optic chiasma was normal in morphology and signal intensity (Fig. 8). She had no polyuria postoperatively and urine output remained normal. Hence, no further evaluation of posterior pituitary function was performed. Anti TPO antibodies were 36 IU/L (< 40), antitissue transglutaminase antibodies were negative. CECT chest was normal. A diagnosis of lymphocytic hypothalamitis with involvement of optic chiasma and thalamus was made. She was started on thyroxin replacement. For the residual lesion, she was planned to be treated with prednisolone 40 mg for four weeks followed by tapering of steroids and subsequently replacement with hydrocortisone. At home, she developed febrile illness and local practitioner stopped steroid replacement, following which she developed vomiting, loose motion and hypotension, and succumbed to probable acute adrenal crisis.

DISCUSSION

Autoimmune hypothalamicitis is a well-known entity.1 These patients present with central diabetes insipidus due to auto antibodies directed against vasopressin secreting cells in hypothalamus.2 These patients can have other associated autoimmune diseases.1,3 An isolated case of autoimmune

Fig. 5: Immunohistochemistry staining, 100X magnification, positive CD 20 immunostaining showing dense B-lymphocytic infiltrates

Fig. 6: Immunohistochemistry staining, 100X magnification, positive CD 3 immunostaining showing T-lymphocytic infiltrates

Fig. 7: Immunohistochemistry staining, 100X magnification, positive CD 68 immunostaining showing histiocyte infiltrates

Fig. 8: Postoperative magnetic resonant imaging: T2-weighted images in coronal section, showing marked decrease in the size of the hyperintense lesion. The pituitary is normal with preserved posterior pituitary bright spot.
hypothalamicitis has been reported in a 70-year-old female who presented with DI with partial anterior pituitary hormone deficiency. In that case, diagnosis was presumed and was based on exclusion of other diseases and response to high dose methylprednisolone and azathioprine. At times the hypothalamus is involved in patients with lymphocytic hypophysitis due to extension of inflammatory process to the structures surrounding pituitary. LH with hypothalamicitis was reported in 69-year-old female who presented with DI and anterior hormone deficiency, and diagnosis was based on imaging and response to glucocorticoids treatment. Ouma and Farell report a case of lymphocytic infundibuloneurohypophysitis in a nulliparous woman who presented with central DI, panhypopituitarism, and visual impairment due to suprasellar mass and involvement of the infundibulum, hypothalamus, optic tracts and chiasma that was managed with glucocorticoids. Biswas et al reported a case of recurrent LH hypophysitis in a nulliparous woman with presented with central DI, panhypopituitarism, and visual impairment due to suprasellar mass and involvement of the infundibulum, hypothalamus, optic tracts and chiasma that was managed with glucocorticoids. In most of the cases, diagnosis of hypothalamicitis was based on MRI findings delineating involvement of pituitary, hypothalamus or surrounding structure.

Our patient primarily presented with signs and symptoms of visual deterioration and raised intracranial tension and suprasellar mass on CT scan. Further examination and evaluation revealed evidence of partial pituitary deficiency (secondary hypogonadism, and hypoadrenalinism). There was no evidence of DI historically or on laboratory assessment. Diagnosis of isolated hypothalamicitis was based on MRI involvement and histological evidence. In our patient, the preoperative MRI image clearly demarcates pituitary from the suprasellar mass (see Fig. 1). Hence, we presume it to be a case of isolated lymphocytic hypothalamicitis. In patients with LH, the MRI image characteristically shows symmetric enlargement of pituitary gland, thickened but undisplaced stalk, intact sellar floor, absent posterior pituitary bright spot, precontrast homogeneity, a strong and homogenous enhancement similar to cavernous sinus and a dural tail, which were absent in our case. However, pituitary biopsy was not taken, hence, microscopic involvement of pituitary cannot be ruled out with certainty. Another limitation was inability to perform dynamic testing with hypothalamic releasing hormones due to nonavailability.

The patient in discussion had many unusual findings. Firstly, she was only 18 years of age, whereas other two cases described in literature were about 70 years of age. Moreover, patients with LH present in fourth decade and commonly in peripartum period. Secondly, patient did not have DI in spite of involvement of hypothalamus, which has been described universally. Thirdly, such large cystic lesion has been rarely described. Fourthly, the lesion spared the pituitary and infundibulum. Hence, it is speculated that anterior pituitary dysfunction could be consequent to deficiency of hypothalamic releasing hormones due to the involvement of hypothalamic nuclei or microscopic involvement of anterior pituitary. Contrary to LH, where ACTH and TSH deficiency appear before gonadotrophin deficiency, our patient had gonadotrophin and ACTH deficiency and thyroid functions were normal preoperatively.

Rapid response to steroids in preoperative and postoperative period in our patient can be due to decongestive effect, however, it could be due to reduction in size of lesion and probably points towards an autoimmune etiology. LH results from an autoimmune process with autoantigens targeted against pituitary tissues. Vasopressin cell antibodies have been demonstrated in patients with DI. Similarly, it would be tempting to hypothesize that lymphocytic hypothalamicitis resulted from either primary cell-mediated immunity with secondary antibody response to released antigen or primary antibodies directed against the cells in the hypothalamic nuclei. Similar hypothesis was put forward to explain idiopathic deficiencies of various hormones of pituitary origin. In our patient, histopathology showed dense lymphocyte infiltrate which were predominantly B and T lymphocytes on immunohistochemistry. Similar finding has been described in LH where pituitary shows mixed T and B lymphocyte aggregate and occasionally plasma cells, histiocytes, eosinophils and neutrophils with or without fibrosis. It is also interesting to note that the patient had selective involvement of hypothalamic nuclei as evidenced by lack of symptoms of DI.

Hyperprolactinemia can be explained by the involvement of the dopaminergic cells in the hypothalamus leading to disinhibition of prolactin regulation. Hyperprolactinemia in LH is caused by multiple factors. Firstly, decrease in dopamine delivery to pituitary by stalk compression due to suprasellar inflammatory mass and failure of hypothalamic dopamine production due to inflammatory lesion. Secondly, presence of antibodies to prolactin secreting cells stimulating the synthesis and secretion of prolactin or causing necrosis and release of prolactin from lactotrophs.

Though LH is a self-limiting condition and 50% of patients recover pituitary functions, most of the prospectively diagnosed cases require some form of treatment. Similarly, most of the suspected cases of lymphocytic hypothalamicitis were managed medically with pulse methylprednisolone, oral prednisolone or immunosuppressive drugs. Patients with visual impairment might require surgical intervention as was performed in our case. Gamma knife surgery has also been used to treat LH.

Outcome in our patient was tragic; as she belonged to remote rural village, where local practitioners usually belong to alternative medicine with little insight into such rare disease. Patient was educated and advised not to stop medicine, but stopped leading to unfortunate outcome.

Screening of literature did not reveal any case of isolated lymphocytic hypothalamicitis presenting as visual impairment with hypopituitarism without DI. We assume that this is the first reported case of isolated lymphocytic hypothalamicitis.

To conclude, in a patient presenting with headache, visual symptoms and hypopituitarism and a suprasellar mass with MRI characteristics matching that of LH, lymphocytic hypothalamicitis
should be considered in differential diagnosis. These patients may benefit from course of steroids and surgery can be avoided.

REFERENCES