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Case Report Open Access

Langerhans Cell Histiocytosis: A Rare Cause of Central Diabetes Insipidus

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Abstract

Objective: To report adult patients with Langerhans cell histiocytosis who presented with a recent onset of polyuria, secondary amenorrhea and galactorrhea.

Methods: We report the clinical presentations, laboratory test results, imaging findings, histological findings and clinical courses of two cases of adult Langerhans cell histiocytosis.

Results: Our evaluation revealed the presence of central diabetes insipidus. Magnetic resonance imaging of the pituitary showed a thickening of the pituitary stalk. The skeleton survey, chest radiography and biochemistry revealed an osteolytic lesion at the frontal bone only in the first case; the other case was within normal limits. A biopsy was performed at the frontal bone in the first case and at the pituitary stalk in the other case. The pathologic examination confirmed the diagnosis of Langerhans cell histiocytosis. Replacement therapy with an intranasal administration of desmopressin can resolve symptoms. The stalk lesion decreased in size without specific treatment.

Conclusions: We reported two cases of adult Langerhans cell histiocytosis. These patients presented with central diabetes insipidus and galactorrhea. Both MRI findings revealed a unifocal infiltration of the infundibulum. The pathologic examination confirmed the diagnosis of Langerhans cell histiocytosis. Replacement therapy with an intranasal administration of desmopressin helped resolve symptoms. The stalk lesion decreased in size without specific treatment. Long-term follow up with proper supplementation to correct hormonal deficiencies may be the proper management in patients with isolated sellar or bone involvement that frequently experience a slower progression of the disease.

Keywords: Central diabetes insipidus; Polyuria, Langerhans cell histiocytosis, Thickening of pituitary stalk

Introduction

Central diabetes insipidus (CDI) is a disorder that is characterized by polyuria, polydipsia and the presence of hypotonic urine as a result of the inability to secrete or to synthesize vasopressin in the neurohypophyseal system [1]. The etiology of CDI comprises a variety of diseases that infiltrate and destroy the posterior pituitary, pituitary stalk, or hypothalamus. We report two young women with an acute onset of CDI, in whom magnetic resonance imaging (MRI) revealed a thickening of the pituitary stalk [2]. Langerhans cell histiocytosis (LCH) had been diagnosed as the cause of CDI in these two patients.

Case 1

A 22-year-old woman presented with polydipsia, polyuria and secondary amenorrhea for 4 months. Physical examination revealed only galactorrhea. Other physical examinations were within normal limits. Her 24 h urine output was 7 liters. Her laboratory results revealed water diuresis with a urine specific gravity of 1.001 and hypernatremia. Her blood chemistries, including the serum level of calcium, glucose and creatinine, were normal. A water deprivation and vasopressin test was performed. For this test, at the end point 11 hr later, water-deprived patients with CDI will respond to an exogenous desmopressin administration by concentrating their urine osmolarity, exceeding 50% above the baseline (Table 1). The water deprivation and vasopressin test confirmed the diagnosis of CDI. Hormone evaluation demonstrated hyperprolactinemia (prolactin level of 46.39 ng/ml; normal range: 4.79-23.3 ng/ml) with normal cortisol, thyroid and gonadotropin levels.

An MRI of the pituitary revealed a thickening of the pituitary stalk (4.4 mm. in diameter), an absence of the posterior bright spot on T1-weighted imaging and a normal signal intensity of the pituitary gland (Figure 1 A-D).

Because LCH is one of the causes of pituitary stalk thickening, a bone survey was performed. The bone survey revealed a single osteolytic lesion at frontal bone of skull (Figure 1 E-F). Computerized tomography (CT) was performed and showed extra-axial soft tissue forming (measuring about 1.1 x 2.0 cm), which was associated with osteolytic bony destruction at right frontal region (Figure 1 G-H).

A biopsy at the right frontal bone was performed and revealed LCH (Figure 2). The patient received intranasal desmopressin treatment, which resulted in the resolution of polyuria. She did not receive any specific treatment for LCH. After follow-up period for 2 years, her galactorrhea improved and her prolactin level normalized without any change in other anterior pituitary hormone level. The follow-up imaging as assessed by a film skull and an MRI of the pituitary also demonstrated a decrease in the size of the pituitary stalk and osteolytic lesion at frontal bone (Figure 1 I-L).

Case 2

A 26-year-old woman presented with polyuria, nocturia, and secondary amenorrhea as well as weight loss of 5 kg in one month. Physical examination revealed galactorrhea. Other results were within normal range. Laboratory analyses showed water diuresis with

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hypernatremia. A water deprivation and vasopressin test confirmed the diagnosis of CDI. Other pituitary hormones were within normal limits.

An MRI of the pituitary demonstrated a round and thick infundibular mass, 5 mm in diameter (Figure 3). The pituitary gland showed homogenous enhancement relative to the normal size, position and signal of the posterior bright spot. Because LCH and germ cell tumors were possible causes of the thickening of the pituitary stalk, a bone survey and serum tumor marker were performed but showed no abnormality.

Times	Body weight (kg.)	Urine volume (cc.)	Urine osmolality (mOsmol/kg H20)	Serum sodium (mmol/L)	Serum osmolality (mOsmol/kg H20)	management
baseline	39.5	720	108	138	310	
5 hr	38.6	180	-	146	325	
6 hr	38.4	180	123	-	-	
7 hr	38.2	160	132	-	-	
8 hr	37.9	210	138	-	-	
9 hr	38	200	141	-	-	
10 hr	37.1	160	74			
11 hr	37	190	132	154	290	DDAVP 0.1 cc intranasal
12 hr	-	50	349	-	-	
13 hr	-	30	535	-	-	
14 hr	-	35	558	-	-	
15 hr	-	30	524	-	-	-

DDAVP; desmopressin, hr; hour, Kg; kilogram, mmol/L; millimoles per liter, mOsmol/kg; millimoles per kilogram

Table 1: Water deprivation testing.

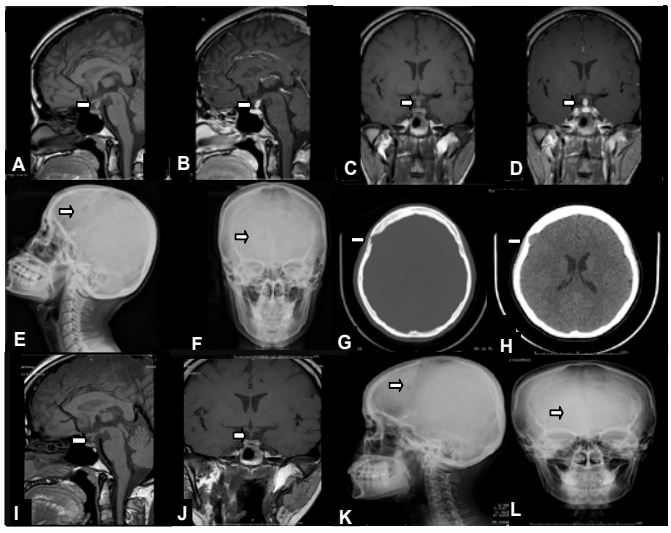

Figure 1: Pituitary stalk thickening and osteolytic lesion at patient's skull at diagnosis and 2 years later. Magnetic resonance imaging of the pituitary demonstrated an enlarged pituitary stalk (4.4 mm) (arrow) without a demonstrated posterior bright spot. A and B) T1W sagittal view without and with Gadolinium, respectively; C and D) T1W coronal view without and with Gadolinium, respectively. E and F) Plain skull film demonstrated osteolytic lesion (arrow). G and H) A computerized tomography brain bone window view demonstrated an extra-axial soft tissue forming associated with osteolytic bony destruction. I and J) T1W sagittal and coronal view without Gadolinium of the patients, 2 year after the diagnosis. K and L) Follow-up plain skull at 2 years later demonstrated improved osteolytic lesion (arrow).

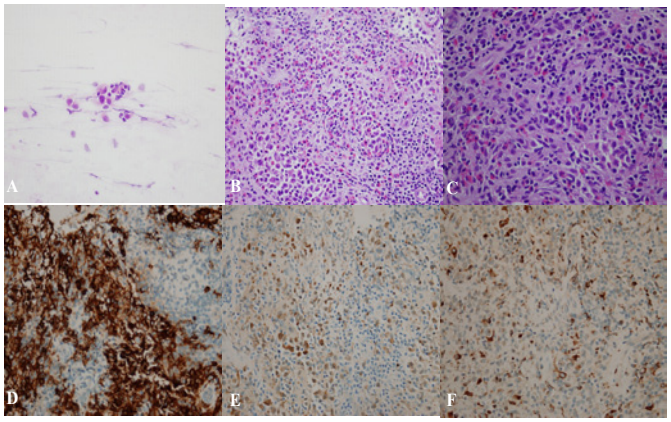

Figure 2: Pathology of skull bone biopsy revealed langerhans cell histiocytosis. A) The squash technique revealed Langerhans cells in which histiocyte-like-cells contained round to oval nuclei with finely granular nuclear chromatin. Most of them show indistinct nucleoli. Grooved and cleaved nuclei are common. A few small lymphocytes are present in the background. (H&E Squash technique, x400). B) Langerhans cell histiocytosis. Langerhans cells are present in a background of mixed inflammatory cells composed of eosinophils, lymphocytes, plasma cells, and neutrophils (H&E, x400). C) Langerhans cell histiocytosis. Higher magnification reveals characteristic folded/convoluted nuclei of the Langerhans cells. (H&E, x600) D) Immunoperoxidase staining for CD1a (x400), E) S100 protein and CD68 and F) highlight Langerhans cell (CD1a, x400).

Figure 3: Pituitary stalk thickening at diagnosis and decreased size of the pituitary stalk after a 6-year follow up. Magnetic resonance imaging of pituitary at the diagnosis revealed an enlarged pituitary stalk of 7 x 6 x 5 mm (arrow) with a demonstrated posterior bright spot. A and B) T1W sagittal view without and with Gadolinium, respectively; C and D) T1W coronal view without and with Gadolinium, respectively. Magnetic resonance imaging of pituitary 6 years after diagnosis demonstrated a reduction in the size of the pituitary nodule at pituitary stalk from 7 x 6 x 5 mm to 2 mm. (arrow) and loss of posterior bright spot. E and F) T1W sagittal view without and with Gadolinium, respectively; G and H) T1W coronal view without and with Gadolinium, respectively.

The patient had been diagnosed with CDI and treated with intranasal desmopressin. The 10-month follow-up MRI of the pituitary revealed a progressive thickening of the pituitary stalk of 7 x 6 x 5 mm. Thus, a pituitary stalk biopsy through right front temporal craniotomy was performed and revealed LCH (Figure not shown). She received intranasal desmopressin treatment without specific treatment for LCH. Yearly follow-up MRIs of the pituitary gland and hormone levels revealed a significant decrease in pituitary stalk thickening (Figure 3 E-H); however, there was no change in her pituitary functions.

Discussion

We report two young patients who presented with central diabetes

insipidus and galactorrhea. Central diabetes insipidus is rare in general population with an estimated prevalence of 1:25,000 [3]. Any disease process involving the hypothalamus or pituitary stalk can lead to CDI. The etiologies of CDI include idiopathic category (42%), neoplasm (28%), infection or inflammation (13%), trauma (5%) and others (12%) [4]. The MRI of the pituitary revealed a thickening of the pituitary stalk in these patients together with the clinical manifestations prompt the differential diagnosis of germinoma, craniopharyngioma, sarcoidosis, tuberculosis, lymphocytic infundibulo-hypophysitis and Langerhans cell histiocytosis [1,4]. Histology confirmed the diagnosis of Langerhans cell histiocytosis in our patients. Langerhans cell histiocytosis has been reported to be the cause of CDI only in 6-15 % of cases [5,6].

LCH is a rare disease that is characterized by the aberrant proliferation of specific dendritic cells. Langerhans cells belong to the monocyte-macrophage system [7]. The normal epidermal Langerhans cell is an antigen-presenting cell that is characterized by the intracytoplasmic Birbeck granule and by the expression of CD1a glycoprotein [8]. These cells can infiltrate and destroy many tissues, especially bone, lung, and skin tissues, and the hypothalamic-pituitary axis. They are also found in the liver, spleen and lymph nodes, but with less frequency. This disease usually considered to be a disease of childhood, however, the diagnosis is frequently made in adulthood [9]. Moreover, many cases of childhood onset progress into adult life [10]. To date, many cases of the adult onset LCH have been reported. The pathophysiology of LCH is still unknown. The course of the disease is fairly unpredictable and varies from spontaneous resolution or progress to a debilitating form, which compromises the vital functions with occasionally fatal consequences [11].

LCH is more often encountered in children, with a peak age range of 1–3 years. The incidence is 3–5 cases per million per year [12]. Adult LCH is uncommon with an estimated prevalence of 1–2 cases per million. LCH in adults can develop at any age, but the mean age at diagnosis is 33 years [13]. Recent studies [9,14,15] have reported that as many as 30-39% of diagnosed cases in adults depend on the age of the included population. LCH in adults has different clinical features than LCH in children. Skin, lung and bone involvement and CDI are common manifestations with adult LCH whereas the involvement of the liver, spleen, lymph nodes and bone marrow is much less frequent [16].

The hypothalamic-pituitary system is involved in 5-50% of child cases of LCH and 14% of adult patients with LCH. Central diabetes insipidus is the most common manifestation of endocrine dysfunction [9] and usually develops within a year after the diagnosis of LCH. Central diabetes insipidus developed in 17-25% of children with LCH and 14-29.6% of adult onset LCH [9,17]. In fact, CDI can also be the first presenting symptom of LCH [2,18], as was the case with our patients. Several pathogenesis of CDI have been postulated including an autoimmune process that involves antibodies reacting against vasopressin, LCH-infiltration and scarring in the hypothalamic pituitary area [6,19,20]. CDI is usually permanent, and the patients may require desmopressin treatment [2,18,19]. Bone, especially skull, involvement is the most common site of LCH involvement [15]. In a study from the Mayo clinic [9], for 44 patients who presented with CDI, 68% of the coexisting LCH was found most frequently in bone, which is similar to our first case.

MRI of the pituitary plays an important role in diagnosing of patients with CDI. Loss of physiological hyper-intense signal of the posterior pituitary (bright spot) on T1-weight imaging is the most common finding in LCH patients with CDI. The second most common finding is a thickening of the pituitary stalk of more than 3.5 mm. Pituitary stalk thickening can be found in 50-70% of patients with LCH at the initial presentation or at follow-up examinations, and it can be found before the onset of CDI [2]. A biopsy of the pituitary stalk is an invasive and risky procedure; thus, it is preferable to establish the diagnosis by the detection and biopsy of an extra-cranial lesion. A careful search for extra-cranial lesions should be performed.

LCH in adults may run a relatively innocuous course [21]. However, some patients with LCH presenting with DI are high risk for the development of anterior pituitary deficiency and neurodegeneration (ND), especially when associated with abnormal pituitary imaging. Moreover, there is possibility of re-growth of the hypothalamic-pituitary mass and cause visual impairment. Because of heterogeneity in the course of the disease, the treatment of the patients is still controversy. In some patients with isolated sellar or bone involvement frequently experience a more gradual disease progression and long survival, so the conservative treatment is one of the choice of treatment in these patients [17]. Clinical monitoring, regular MRI surveillance and proper replacement of hormones that are lacking are the most important treatments for improving the patient's quality of life. Systemic chemotherapy is only initiated when other extracranial LCH lesions are present or the patients with pronounced space-occupying lesions in the hypothalamic region. Recent study [22, 23] showed that in patients with masked thickening of pituitary stalk, with a maximum diameter of more than 6.5 mm, systemic LCH protocol chemotherapy lead to a reduction of tumor size in most cases. However, the prevention of permanent endocrine deficiency and LCH associated neurodegenerative syndrome with the current treatment is still unclear. The lack of effectiveness of current chemotherapy may attributable to the treatment was given later in the course of the disease [22]. It remains unknown whether early therapeutic intervention would be effective in prevention of endocrinopathies and neurodegenerative syndrome or modification of the clinical course of the disease. Due to the lack of standard treatment regimen, long-term clinical follow up, neuropsychological testing and regular MRI of the pituitary are fundamental in LCH patients presenting with DI. Systemic chemotherapy and/or radiotherapy should be considered if the patients have pronounced space-occupying lesions in the hypothalamic region or have progression of the disease.

Conclusion

We report two cases of adult Langerhans cell histiocytosis who presented with central diabetes insipidus and galactorrhea. MRI findings for both patients revealed a unifocal infiltration of the infundibulum. The pathology examination led to the diagnosis of LCH. Replacement therapy with intranasal administration of desmopressin helped resolve symptoms. The stalk lesion decreased in size without specific treatment. Long-term follow up with proper supplementation to correct hormonal deficiencies may be the proper management in patients with isolated sellar or bone involvement that frequently experience a slower progression of the disease.

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