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**
An MRI of the pituitary revealed a thickening of the pituitary stalk. The skeleton survey, chest radiography and biochemistry revealed an osteolytic lesion at 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. 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).

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

**References**


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Received November 17, 2012; Accepted February 10, 2012; Published February 14, 2012

**Citation:** Srivanichakorn W, Tanboon J, Srijivitkamol A (2012) Langerhans Cell Histiocytosis: A Rare Cause of Central Diabetes Insipidus. Internal Med: Open Access 2:107. doi:10.4172/2165-8048.1000107

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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 known causes of the thickening of the pituitary stalk, a bone survey and serum tumor marker were performed but showed no abnormality.

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 4).

Discussion

We report two young patients who presented with central diabetes insipidus.
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%), neoplasms (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, crianiopharyngioma, 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 at 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 controversial. 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 chemotherapym 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.

Acknowledgement

We wish to acknowledge Assoc. Prof. Pipat Chiewvit M.D., Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University.
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