An Elderly Patient with Transient Diabetes Insipidus Associated with Lymphocytic Infundibulo-Neurohypophysitis

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Abstract. We present the eldest case ever reported of central diabetes insipidus (DI) associated with infundibulo-neurohypophysitis. A 77-year old woman, who complained of recent development of excessive thirst, polyuria and polydipsia, was referred to our hospital. The daily urine volume was markedly increased to 6 L. DDAVP administration effectively reduced urine volume and increased urine osmolality. The loading test using high-osmolar sodium chloride showed impaired excretion of vasopressin discordant with plasma osmolar changes. The anterior pituitary function was normal. Pituitary magnetic resonance imaging (MRI) showed thickening of the pituitary stalk and a lack of high-intensity signal of the neurohypophysis on T1-weighted images, suggestive of lymphocytic infundibulo-neurohypophysitis. The thickness of pituitary stalk on MRI improved 6 months later. DI was controlled with DDAVP for 40 days. This was followed by stabilization of the daily urine volume to less than 2.5 L without DDAVP. Our case is the eldest case of central DI associated with infundibulo-neurohypophysitis. The rapid remission of pituitary changes on MRI provides an insight that spontaneously partial remission of central DI may occur, resulting in transient polyuria and polydipsia.

Key words: Transient diabetes insipidus, Lymphocytic infundibulo-neurohypophysitis, High-aged onset, Magnetic resonance imaging (MRI)

In 1993, Imura et al. [1] proposed a new disease entity called “lymphocytic infundibulo-neurohypophysitis” (LIN), which was different from the classical lymphocytic adenohypophysitis (LA). The LIN lesion specifically involves the neurohypophysis of the pituitary, causing diabetes insipidus (DI). The diagnosis of LIN is usually based on the findings of magnetic resonance imaging (MRI) consisting of thickening of the pituitary stalk and enlargement of the posterior lobe without hyperintense signal, which usually presents as self-limiting and results in permanent DI [1, 2]. However, the pathogenesis of LIN including the possible involvement of autoimmune mechanisms has yet to be established. In contrast, the pathogenesis of LA is thought to be due to an autoimmune disease of the pituitary gland, which is associated with pregnancy [3].

We present here the eldest case of central DI probably associated with LIN. This interesting case exhibited transient polyuria caused by spontaneously partial remission of central DI.

Case Report

In February 1998, a 77-year-old Japanese woman consulted a clinic, complaining of recent onset of excessive thirst and headache. Initially, the patient was treated as a common cold case but the symptoms failed to respond to conservative therapy. Subse-
sequently, she suddenly developed a combination of polydipsia and polyuria of up to 6 L/day, followed by palpitation and low grade fever. She was referred to our hospital and admitted in April 1998 for further management. Her past medical history was negative, including no incidence of head trauma, except for hypertension diagnosed three years before the current presentation. Blood pressure was controlled by benazepril hydrochloride (2.5 mg/day). Her family history was not peculiar. On admission, the patient weighed 44 kg and was 145 cm tall. The blood pressure was 144/82 mm Hg, pulse rate 72 bpm regular, and body temperature 37.4°C. There were no abnormal signs other than dry mouth and skin on physical examination including ophthalmological and neurological examinations.

Laboratory data on admission showed the following: white blood cells, 5,000/μL (normal, 3.0–9.4); red blood cells, 4.21 × 10⁶/μL (normal, 3.7–4.9); hemoglobin, 13.7 g/dL (normal, 11.5–14.5); hematocrit, 41.4% (normal, 35–44); C-reactive protein, 0.3 mg/dL (normal, <0.3); and erythrocyte sedimentation rate, 11 mm/h. Serum sodium and chloride concentrations were elevated at 155 mmol/L (normal, 136–144) and 114 mmol/L (normal, 102–110), respectively, while serum potassium level was normal at 3.7 mmol/L (normal, 3.7–4.9). Urinalysis was normal but urinary sodium, potassium and chloride levels were low at 2 g/day (normal, 4–8), 1.5 g/day (normal, 1.5–2.5) and 3 g/day (normal, 6–12), respectively. Renal and liver function tests were normal. Fasting blood glucose (105 mg/dL; normal, 65–105) and hemoglobin Alc (5.7%; normal, 4.6–6.3) levels also were normal.

Urinary and plasma osmolality were 153 and 299 mOsM/kg with free oral water intake, respectively (Table 1). Plasma vasopressin level, measured by radioimmunoassay, was low (1.0 pg/mL), when plasma osmolality was 299 mOsM/kg. Administration of 10 μg DDAVP (desmopressin acetate) effectively reduced sequential hourly urine volume (244 to 10 mL after 3 hours) and increased hourly urine osmolality (186 to 483 mOsM/kg after 3 hours). A loading test of 5% sodium chloride (0.24 mL/kg-bw/min for 10 min) showed little increase in arginine vasopressin (AVP) level in response to the high plasma osmolality (Fig. 1a). Basal anterior pituitary

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**Table 1. Endocrine examination data on admission**

<table>
<thead>
<tr>
<th></th>
<th>AVP</th>
<th>P-osmolality</th>
<th>U-osmolality</th>
<th>ACTH</th>
<th>Cortisol</th>
<th>Aldosterone</th>
<th>PRA</th>
<th>Urine 17-OHCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 pg/mL (0.8–6.3)</td>
<td>299 mOsM/kg (285–295)</td>
<td>153 mOsM/kg (50–1400)</td>
<td>38.2 pg/mL (4.4–48)</td>
<td>17.0 pg/dL (5–21)</td>
<td>112 pg/mL (57–150)</td>
<td>2.6 ng/mL/h (0.3–2.9)</td>
<td>5.0 mg/day (2.6–7.8)</td>
</tr>
<tr>
<td>TSH</td>
<td>1.37 μU/mL (0.3–4.1)</td>
<td>FT3</td>
<td>2.44 pg/mL (1.7–3.7)</td>
<td>FT4</td>
<td>1.33 ng/dL (0.9–1.7)</td>
<td>GH</td>
<td>2.2 ng/mL (0.3–9)</td>
<td>PRl</td>
</tr>
</tbody>
</table>

AVP, arginine vasopressin; P-, plasma; U-, urine; PRA, plasma renin activity. Data in parentheses represent the normal range.
function tests were normal (Table 1). Basal serum cortisol and plasma aldosterone concentrations and plasma renin activity were also normal and thyroid function tests were normal. Serum antipituitary antibodies measured with rat pituitary cytoplasmic antigens (PCA) were not detected. Antinuclear, antithyroglobulin and antithyroid microsomal antibodies were also negative. Cranial MRI showed thickening of the pituitary stalk and absence of a high intensity signal of the neurohypophysis on T1-weighted image (Fig. 2).

After admission, the patient was treated with 5 μg/day of intranasal DDAVP (Fig. 3). This resulted in reduced urine volume but her daily urine volume was fairly variable. Serum sodium level was gradually decreased according to the reduction of urine volume. Cessation of DDAVP administration within the first 40 days of the onset of polyuria resulted in increased urinary volume. However, the patient was able to maintain the urinary volume below 2,500 mL/day after the first 40 days of the onset of polyuria without the use of DDAVP. Six months later, when her daily urine volume was approximately 2,000 mL, 5% sodium chloride loading test was performed again. It showed a partial remission of AVP excretion although a complete recovery was not seen (Fig. 1). The pituitary MRI at that time demonstrated disappearance of the thickening of the pituitary stalk but a persistent lack of the posterior high signal (Fig. 2). At the time of preparation of this report (10 months after the development of polyuria), the patient has been doing well without headache,

Fig. 2. Pituitary MRI findings. Pituitary MRI showed thickening of the pituitary stalk (arrows) and absence of a high intensity signal of the neurohypophysis on T1-weighted image (A). Another pituitary MRI taken 6 months later demonstrates a remission of the thickness of the pituitary stalk but a persistent lack of the posterior high signal (B).
fever, polydipsia or polyuria.

Discussion

Chronic hypernatremia due to inflammation of the neurohypophysis was reported by Saito et al. in 1970 [4]. DI, associated with lymphocytic infiltration limited to the infundibulum, stalk and posterior lobe of the pituitary gland, was also reported by Kojima et al. in 1989 [5]. Their case also showed neuronal loss with gliosis in the supraoptic and paraventricular nuclei [5]. In 1993, Imura et al. [1] confirmed the concept of DI caused by LIN, by describing 9 of 17 patients with DI who showed thickening of the pituitary stalk and enlargement of the neurohypophysis or both on MRI [1]. MRI in these patients also showed the absence of the hyperintense signal which is a characteristic feature of the normal neurohypophysis [6]. The present case was diagnosed as central DI based on the low excretion of AVP even under high-osmolar conditions. The MRI findings of the pituitary were consistent with the above-mentioned characteristics of LIN.

The noticeable finding in the present case was relatively rapid morphological changes in the pituitary stalk. This change spontaneously appeared 6 months after the onset of polyuria. Imura et al. [1] reported that the MRI abnormality of LIN was only observed in patients who had manifested DI for less than 2 years and that the improvement on MRI was shown on the follow-up study 2 to 5 years later. In general, it has been suggested that the inflammatory process of LIN is self-limited and may remit spontaneously in approximately 2 years [1–3]. Moreover, a permanent and persistent DI follows the inflammatory remission probably because of the destruction of neurons [1, 2]. The present case seemed to be a clinically transient DI which lasted approximately 40 days. However, taking into consideration that the high sodium chloride loading test 6 months later showed incomplete recovery of AVP secretion compared with the results on admission, this clinical course would have to be regarded as a partial remission of central DI. As a mechanism of this remission, the pituitary involvement might be limited within the infundibulum and not involve the hypothalamic nuclei, particularly since approximately more than 90% of the magnocellular neurons in the supraoptic nuclei and paraventricular nuclei have to be lost or functionally damaged before DI develops [7]. The maintenance of basal adeno-hypophysial function in the present case was also in agreement with this hypothesis. We previously reported a 60-
year-old woman with transient central DI for 14 days which developed immediately after general anesthesia, whose endocrine data and pituitary MRI findings, including thickening of the infundibulum and lack of posterior high signal, were in agreement with central DI due to LIN [8]. In this previous case, the morphological change on pituitary MRI disappeared two months later. Although we cannot confirm the etiology of this case or the present case because of the lack of proper histological examination, these cases raise the possibility that any reversible change resembling LIN or very weak damage of the infundibulum of the neurohypophysis might be associated with a self-limiting DI and transient thickening of the pituitary stalk. On the discrepancy between the AVP-deficiency and the remission of polyuria, increase in the renal sensitivity to AVP might be implicated in this partial remission since neither her adrenocortical nor renal insufficiency was detected. The change of renal sensitivity to AVP might also be associated with the variability of her urine volume during the DDAVP replacement.

Another interesting aspect of our case is her age at DI onset. A review of the literature showed a total of 40 reported cases who had manifested central DI associated with LIN [1, 4, 5, 10-21]. These cases consist of 12 men and 28 women; with a mean age of 47.3±17.4 years (±SD), including the youngest of 3 years [12] and oldest of 74 years [5]. Apart from LA, which is generally characterized by a close association with apparent autoimmunity or pregnancy [2, 3], the exact pathogenic mechanisms of LIN have yet to be elucidated, except for a few cases suggestive of being associated with pregnancy [15] or autoimmunity [22, 23]. Our case, the eldest case reported so far, who had LIN and manifested a transient central DI, might be a specific variety of idiopathic DI. We cannot completely exclude the possibility that the present case might be necrotizing infundibulo-neurohypophysis, as suggested by Ahmed et al. [24] or lymphocytic hypophysitis involving both adeno- and neuro-hypophysis [16]. To differentiate between these related pathologies, further studies of both the clinical and pathological characteristics are required. Furthermore, we should cautiously follow up this patient, considering the possibility of other disorders involving hypothalamus and pituitary, such as germinoma, histiocytosis X, sarcoidosis, tuberculosis, metastatic tumor and lymphoma [1, 25].

In conclusion, we reported the eldest case of central DI associated with LIN. Polyuria lasted about 40 days, followed by recovery of polyuria and polydipsia. A regression of the thickened infundibulum was evident on pituitary MRI, 6 months after onset of symptoms. This case provides an example of LIN in elderly patients, and emphasizes the importance of careful follow-up, including MRI and endocrine examination, in aged patients with polyuria and polydipsia.

References


