A case of central diabetes insipidus following probable type A/H1N1 influenza infection

Takaaki Kobayashi, Takashi Miwa and Masato Odawara

Division of Diabetes, Metabolism and Endocrinology, Third Department of Internal Medicine, Tokyo Medical University, Tokyo 160-0023, Japan

Abstract. The major causes of central diabetes insipidus (CDI) are neoplastic or infiltrative lesions of the hypothalamus or pituitary gland, severe head injuries, or pituitary or hypothalamic surgery. Lymphocytic infundibuloneurohypophysitis (LINH) is associated with autoimmune inflammatory disease of the pituitary gland, but the exact etiology is unknown. CDI caused by viral infections has been rarely reported. Here, we describe the case of a 22-year-old man who was in good health until 2 months prior to admission, presented with acute development of polyuria and polydipsia, and showed increased urinary volume up to 9000 mL/day. The patient showed elevated serum osmolality and low urine osmolality, with a low level of antidiuretic hormone. Endocrinological findings revealed CDI, but his arterial pituitary function appeared normal. Magnetic resonance imaging revealed significant enlargement of the pituitary stalk. We suspected CDI due to LINH based on non-transsphenoidal biopsy findings. He was diagnosed as type A influenza, and given oral therapeutic agents. However, acute onset of polyuria and polydipsia occurred 10 days after the influenza diagnosis. The available epidemiological information regarding the outbreak of influenza around that time strongly suggested that the patient was infected with the A/H1N1 influenza virus, although this virus had not been detected on polymerase chain reaction testing. In the present case, the autoimmune mechanism of LINH may have been associated with novel influenza A/H1N1 virus infection.

Key words: Central diabetes insipidus, Lymphocytic infundibuloneurohypophysitis, H1N1 influenza

CENTRAL diabetes insipidus (CDI) has been reported to be idiopathic in 30% to 50% of cases, and its pathogenesis remains unclear [1]. Recently, it has been noted that some patients in the acute phase develop lymphocytic infundibuloneurohypophysitis (LINH), suggesting that an autoimmune mechanism is involved in the development of this disease. Here, we report the case of a patient who developed CDI after probable infection with a new type of influenza virus.

Case report

The patient was a 22-year-old male university student. In the first week of September 2009, there was a mass outbreak of influenza in a university sports club that he had joined, and he visited a local clinic because of a low-grade fever on September 10. Since he tested positive for influenza virus type A on a rapid influenza test, he was prescribed oseltamivir phosphate capsules, which resulted in the rapid improvement of his symptoms. From around September 20, he experienced polydipsia and a frequent need to urinate. Since his father had diabetes mellitus, he suspected that he had also developed the disease and visited a local clinic on September 24. Blood tests showed an HbA1c level of 4.9%, and urinalysis did not show any evidence of glycosuria, which excluded the possibility of symptomatic diabetes mellitus. He was therefore followed-up because of this condition. However, he continued to experience polydipsia, polyuria, and these symptoms gradually exacerbated. In November of that year, he experienced nocturia with sleep disturbance, and visited the local clinic again. Since his symptoms suggested diabetes insipidus, the local clinic measured his antidiuretic hormone (ADH) level which was below the detection limit.
Thus, he was referred to our department in mid-November, and admitted for further evaluation and treatment for suspected diabetes insipidus.

On admission, he was 173 cm tall and weighed 69 kg, with a body mass index of 23.1 (although his ideal body weight was 65.9 kg). His blood pressure was 135/83 mm Hg, his body temperature was 36.8°C, his pulse rate was 72 beats/min and regular, and his respiratory rate was 15/min. His palpebral conjunctivae were not anemic, and his bulbar conjunctivae were not icteric. His tongue was not dry. No vascular murmurs were heard in the cervical region. The thyroid gland was not palpable. His heart sounds were clear, with no audible murmurs. Breath sounds were clear, and no rales were heard. The abdomen was flat and soft, and the liver and spleen were not palpable. There was no pretibial edema. He had a history of childhood asthma with episodes of wheezing until middle-school age, but not at or after age 15. His family history showed Parkinson disease and paternal diabetes mellitus (his father was being treated with insulin). He had no history of smoking, and was a social drinker. He was allergic to house dust and cats.

His laboratory data on admission were as follows; blood count: white blood cells, 8600/μL; red blood cells, 456 × 10^4/μL; hemoglobin, 14.6 g/dL; hematocrit, 43.1%; platelets, 23 × 10^4/μL; blood chemistry: total protein, 7.4 g/dL; albumin, 4.4 g/dL; aspartate aminotransferase, 22 U/L; alanine aminotransferase, 21 U/L; γ-glutamyltransferase, 22 U/L; alanine aminotransferase, 21 U/L; lactate dehydrogenase, 171 U/L; alkaline phosphatase, 158 U/L; total cholesterol, 153 mg/dL; HDL-cholesterol, 87 mg/dL; triglyceride, 71 mg/dL; serum glucose, 70 mg/dL; hemoglobin A1c (JCS), 4.8%; blood urea nitrogen, 8.8 mg/dL; creatinine, 0.83 mg/dL; sodium, 140 mEq/L; potassium, 4.0 mEq/L; C-reactive protein, 0.3 mg/dL; human chorionic gonadotropin β, < 0.1 ng/mL; serum osmolarity, 279 mOsm/kg; antinuclear antibody, negative; anti-thyroid peroxidase antibody, (-); thyroid-stimulating hormone receptor antibody, < 1.0; anti-pituitary antibody, (-); anti-influenza-A antibody (CF) × 16; myeloperoxidase antineutrophil cytoplasmic antibody, < 10 U/mL; cytoplasmic-anti-neutrophil cytoplasmic antibody, < 10 U/mL; angiotensin-I-converting enzyme, 8.3I U/L; immunoglobulin G (Ig), 1346 mg/dL; immunoglobulin G4, 34.5 mg/dL (4.8 - 105); urinalysis: sugar (-); protein (-); urine osmolality, 93 mOsm/kg; endocrinological findings: adrenocorticotropic hormone, 45.7 pg/mL; luteinizing hormone, 4.8 mIU/mL; follicle-stimulating hormone, 3.6 mIU/mL; prolactin, 48.2 ng/mL; growth hormone, 0.45 ng/mL; insulin-like growth factor-1, 201 ng/mL; thyroid-stimulating hormone, 4.43 μU/mL; free thyroxine, 1.31 ng/dL; free triiodothyronine, 3.48 pg/mL; antidiuretic hormone, 0.7 pg/mL; cortisol, 18.1 μg/dL; free testosterone, 9.6 ng/mL; dehydroepiandrosterone sulfate, 246 μg/dL.

On admission, the patient was drinking about 10 L of water per day, and urinated every 1-2 hours at night with a daily urinary output of 7-9 L. We performed hypertonic saline and DDA VP tests on December 1 (Table 1). An increase in his serum osmolarity was not accompanied by a corresponding increase in antidiuretic hormone (ADH) secretion, and DDA VP loading resulted in an increase in urine osmolarity; therefore, we diagnosed CDI. On December 2, a three-hormone anterior-pituitary test was performed to evaluate his anterior pituitary function (Table 2). No clear evidence of anterior pituitary dysfunction was found, and his prolactin (PRL) level was high. Therefore, considering the possibility of hypothalamic disorders, we performed an insulin hypoglycemia test (Table 3).

### Table 1 Hypertonic saline test

<table>
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<th>Before loading</th>
<th>After 30 min</th>
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<tr>
<td>Serum osmolarity (mOsm/kg)</td>
<td>283</td>
<td>290</td>
<td>296</td>
<td>297</td>
<td>303</td>
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<tr>
<td>Urine osmolarity (mOsm/kg)</td>
<td>60</td>
<td>82</td>
<td>99</td>
<td>78</td>
<td>96</td>
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<td>Serum sodium (mEq/L)</td>
<td>141</td>
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<td>146</td>
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<td>148</td>
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<tr>
<td>Antidiuretic hormone (pg/mL)</td>
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<td>0.7</td>
<td>0.9</td>
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### Table 2 Three-hormone anterior pituitary test

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<td>ACTH (pg/mL)</td>
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<td>33.6</td>
<td>28.6</td>
<td>19.7</td>
<td>14.5</td>
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<tr>
<td>LH (mIU/mL)</td>
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<td>21.5</td>
<td>18.5</td>
<td>15.8</td>
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<td>FSH (mIU/mL)</td>
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<td>5.1</td>
<td>4.9</td>
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<td>TSH (μU/mL)</td>
<td>2.02</td>
<td>11.94</td>
<td>8.84</td>
<td>6.41</td>
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<tr>
<td>PRL (ng/mL)</td>
<td>68.8</td>
<td>84.9</td>
<td>58.9</td>
<td>45.7</td>
<td>41.5</td>
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</table>
Diabetes insipidus following influenza

His growth hormone (GH) and adrenocorticotropic hormone (ACTH) responses were normal. On the evening of December 4, we started treatment with 5 µg/day desmopressin, and increased the dose to 7.5 µg/day from December 16, while monitoring his fluid intake and urinary output, and aiming to prevent water intoxication. The severity of his symptoms were stabilized by the use of a desmopressin nasal spray (2.5 µg in the morning and 5 µg before bed), and his urinary output was maintained at 1-3 L (Fig.1-A,B Fig.2-A,B).

<table>
<thead>
<tr>
<th>Table 3 Insulin hypoglycemia test</th>
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<tr>
<td>Blood glucose (mg/dL)</td>
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<td>GH (ng/mL)</td>
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<td>ACTH (pg/mL)</td>
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<td>cortisol (µg/dL)</td>
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Fig. 1-A, B Magnetic resonance imaging (MRI) of the pituitary gland.

A plain MRI of the pituitary gland showed the disappearance of a high-intensity signal and enlargement of the pituitary stalk on T1-weighted images.

Fig. 2-A, B Gd-enhanced T1-weighted MRI revealed a diffusely stained pituitary gland and enlarged pituitary stalk.
The present patient received 2 courses of methylprednisolone pulse therapy (1,000 mg/day) for 3 consecutive days, which did not affect the frequency of desmopressin use. After the pulse therapy, magnetic resonance imaging (MRI) at 14 months showed no shrinkage of the diffusely stained pituitary gland and enlarged pituitary stalk in this case.

Discussion

Lymphocytic infundibuloneurohypophysitis (LINH) is considered to be a disease characterized by lymphocytic infiltration of the pituitary stalk and posterior lobe, resulting in CDI. In 1993, Imura et al. noted that many patients showed thickening of the pituitary stalk and enlargement of the posterior pituitary within 2 years of onset of idiopathic diabetes insipidus, and proposed that lymphocytic hypophysitis was a cause of idiopathic diabetes insipidus [2]. Pituitary biopsy is a reliable method of diagnosing this condition. However, in view of the risk of causing serious complications such as liquor rhrea from the commonly used transnasal transethmoidal approach, and the risk of impairing preserved anterior pituitary function, caution should be exercised when performing pituitary biopsy for diagnosis.

The differential diagnosis of diseases that cause CDI includes neoplastic lesions (e.g., germinoma) and granulomatous diseases (e.g., sarcoidosis). In this patient, a plain MRI of the pituitary gland showed the disappearance of a high-intensity signal in the posterior lobe and enlargement of the pituitary stalk on T1-weighted images, and gadolinium (Gd)-enhanced T1-weighted MRI revealed a diffusely stained pituitary gland and enlarged pituitary stalk. These findings did not indicate a clearly neoplastic lesion, and were consistent with LINH. Blood tests were negative for α-fetoprotein (AFP), carcinoembryonic antigen (CEA), and human chorionic gonadotropin β (hCGβ). In germinomas, tumor growth is associated with elevated levels of hCGβ. It was previously reported that, although the blood and cerebrospinal fluid (CSF) levels of hCGβ in a patient as determined by the conventional method were in the normal range, the tumor grew and the hCGβ levels had exceeded the normal range 1 year later, leading to a diagnosis of germinoma [3]. In this regard, an hCGβ assay with a sensitivity of more than 1,000 times that of a conventional assay has been developed [4]. Using this ultrasensitive assay, we measured the levels of hCGβ in the serum and CSF, but observed no abnormal values. CSF examination did not reveal any increase in the number of cells, and his CSF cytology was class 1. Whole-body computed tomography (CT) did not reveal any features suggestive of a primary or metastatic malignancy. Furthermore, serum myeloperoxidase-anti-neutrophil cytoplasmic antibody (P-ANCA), cytoplasmic -anti-neutrophil cytoplasmic antibody (C-ANCA), and angiotensin-converting enzyme (ACE) levels were measured to exclude granulomatous diseases, but the values were within normal limits. These findings strongly suggest LINH, although it was not confirmed by pituitary biopsy. Kristof et al. reported that the presumptive non-invasive diagnosis of lymphocytic hypophysitis is possible in a large proportion of patients [5]. In particular, they diagnosed lymphocytic hypophysitis in 6 of 9 patients by clinical and endocrinological assessments, MRI, and CSF examination without biopsy.

Since the histological definitive diagnosis of LINH requires invasive pituitary biopsy, this has generally only been undertaken in a small proportion of patients, and pituitary tumors have been found in some patients with suspected lymphocytic hypophysitis. Therefore, there has been a growing need for the development of a noninvasive diagnostic method. Sugimura have conducted studies to develop methods for measuring autoantigens and autoantibodies specifically for the diagnosis of LINH [6]. In the present study, similar specimens were also used after written informed consent was obtained from the patient.

LINH has been reported to be frequently associated with autoimmune diseases, although its pathogenesis remains unclear. The patient was negative for antithyroid peroxidase (TPO), anti-thyroglobulin, anti-glutamic acid decarboxylase (GAD), anti-nuclear, and anti-pituitary antibodies. Recent studies have reported that diabetes insipidus may in some cases be an immunoglobulin (IgG) 4-related disease [7, 8] but the serum IgG4 level was not elevated in the present patient.

It is believed that an immune response triggered by viral or bacterial infection is involved in the development of LINH; however, the viruses or bacteria that commonly cause this disease have yet to be identified, partly because of their extremely low incidence. Cases of LINH after meningocencephalitis due to the type A influenza virus or herpes simplex virus were previously reported [9].

In this patient, a blood test performed in December 2009 showed a positive anti-influenza A antibody titer
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In terms of the rapid influenza test results, this finding was consistent with the onset of influenza A virus infection. The patient first became aware of symptoms, apparently caused by diabetes insipidus, 10 days after the detection of influenza infection. Thus, we speculated that this infection-induced autoimmune response resulted in inflammatory changes in the posterior pituitary lobe, leading to the onset of the symptoms of diabetes insipidus.

Influenza developed in this patient between September 7 and 13, 2009 (on week 37). According to the data compiled by the Infectious Disease Surveillance Center of the National Institute of Infectious Diseases, the new influenza A/H1N1 virus was isolated and identified in 419 of 421 patients. At approximately the same time, the Tokyo Metropolitan Government reported that the influenza A/H1N1 virus had been isolated from all 30 influenza A-positive patients. Since no influenza A/H1N1 virus was isolated from the patient in the current report, it was not possible to definitively diagnose the same new-type influenza. However, the available epidemiological information on the outbreak of influenza around that time strongly suggests that the present patient was infected with the influenza A/H1N1 virus.

The recent popularization of rapid influenza test kits has facilitated the diagnosis of influenza, and the number of influenza-infected patients has increased. However, markedly fewer cases of diabetes insipidus or autoimmune infundibuloneurohypophysitis following influenza infection have been reported, and our search of reports in the literature revealed no cases of diabetes insipidus developing after the oral intake of the anti-influenza drug oseltamivir phosphate, which was administered orally to the present patient.

Although there is no established treatment for LINH, treatment with steroids has been attempted. The oral administration of a pharmacological dose of prednisolone was reported to improve pituitary enlargement and diabetes insipidus [10]. On the other hand, pulse therapy with methylprednisolone was reportedly ineffective [11]. The present patient received 2 courses of methylprednisolone pulse therapy (1,000 mg/day) for 3 consecutive days, which did not affect the frequency of desmopressin use.

Itagaki et al. reported that steroid therapy for LINH must be started as early as possible to clinically improve diabetes insipidus. They suggested that it is particularly important that steroid therapy should be administered within 2 months of the onset of symptoms [12]. In the present case, 4 months passed from the onset of symptoms to the steroid therapy. Early diagnosis and steroid therapy could have achieved remission of diabetes insipidus.

In conclusion, we report a case of CDI following probable type A/H1N1 influenza infection. In this case, the autoimmune mechanism of LINH may have been associated with novel influenza A/H1N1 virus infection. Although there was a possibility that the influenza was incidentally complicated by LINH and diabetes insipidus during a relatively short period of 10 days, we consider this case interesting because the incidence of influenza A/H1N1 continues to increase in 2011.

Acknowledgments

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References


