# Aquaporin-4 antibody positive neuromyelitis optica with syndrome of inappropriate antidiuretic hormone secretion

*Xiao-Fan You,* MD, *Wei Qin,* MD, *Wen-Li Hu,* MD.


## ABSTRACT

يعد التهاب النخاع والعصب البصري (Neuromyelitis optica) من الأمراض التي تصاحب اضطرابات الغدد الصماء مثل انقطاع الحيض، ودر اللبن دون وجود إرضاع، والسكري. غير أن ارتباط هذا المرض بمتلازمة خلل إفراز الهرمون المضاد لإدرار البول يعد نادراً جداً. نستعرض في هذا المقال حالة مريضة صينية مُصابة بالتهاب النخاع والعصب البصري مع متلازمة خلل إفراز الهرمون المُضاد لإدرار البول. أظهرت نتائج التحليل بأنها كانت حاملة للجسم المضاد أكوابورين- 4 (aquaporin-4)، وقد يكون اضطراب هرمونات الغدة النخامية (اضطراب وطائي المِنشأ) من العوامل المسببة لظهور متلازمة خلل إفراز الهرمون المُضاد لإدرار البول.

Neuromyelitis optica (NMO) has been reported to be associated with endocrinopathies, such as amenorrhea, galactorrhea, and diabetes mellitus. However, its association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is extremely rare. We herein report an adult case of NMO with SIADH in a female Chinese patient. The patient was aquaporin-4 antibody positive, and her hypothalamic dysfunction may have been related to the development of SIADH.


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*From the Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China.*

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*Address correspondence and reprint request to: Dr. Wen-Li Hu, Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing 100020, China. Tel. +86 (10) 85231391 / +86-13466718596. Fax. +86 (10) 85231514. E-mail: cyneurology@gmail.com*

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the CNS mainly affecting the optic nerves and spinal cord. The aquaporin-4 (AQP4) antibody has been described as a relatively sensitive and specific marker for NMO.[1] There are reports demonstrating that NMO is associated with endocrinopathies, including amenorrhea, galactorrhea, diabetes mellitus, and hypothyroidism.[2-4] However, hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) rarely occurs in NMO. On literature review, we found only one case described of a pediatric NMO patient.[5] In this report, we describe an adult case of NMO with positive AQP4 antibody that developed SIADH. Our objective in reporting this particular case is to report the early recognition and treatment of NMO associated with SIADH.

**Case Report.** A 56-year-old Chinese woman was admitted to our hospital in October 2004. She completely lost vision in her left eye. A brain MRI showed no abnormal findings. She was diagnosed with optic neuritis and treated with corticosteroids (a 5-day course of 1000 mg methylprednisolone, followed by dose tapering). Her vision resolved completely. Two months later, she developed another episode of optic neuritis of her right eye resulting in total blindness. An MRI revealed T2 hyperintense signals in the right optic nerve (**Figure 1A**). She again had a good recovery after corticosteroid therapy. In April 2005, she presented with weakness in all 4 limbs, numbness, and dysuria. The symptoms progressed to complete quadriplegia in 3 days. A neurological examination revealed sensory loss below the T2 level, and her muscle strength was 3/5 in arms and 1/5 in legs. Babinski signs presented bilaterally. A spine MRI revealed a cervical cord lesion extending from C6 to T3 without brain abnormalities beyond the optic nerves (**Figure 1B**). Her CSF was normal and revealed a white blood cell count (WBC) of $2\times10^6$ WBC/L, protein of 40 mg/dl, glucose of 60 mg/dl, and no oligoclonal bands. The brainstem auditory evoked potential was normal. The visual evoked potential revealed a wave of P100 of borderline latencies with low amplitudes. The diagnosis of NMO was made. Her symptoms partially improved after treatment with methylprednisolone and immunoglobulin (0.4 g/kg for 5 days).

In June 2007, she was admitted again suffering from a cough, sore throat, and a fever of approximately

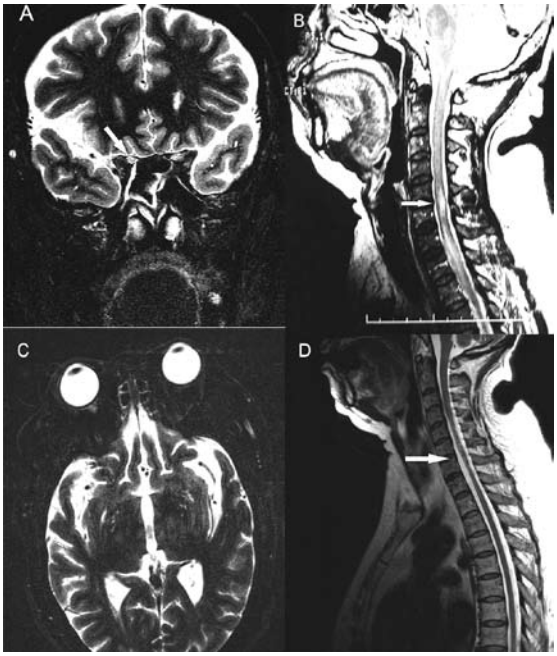


**Figure 1 -** Magnetic resonance imaging findings: **A**) A coronal T2-weighted image showing hyperintense signals in the right optic nerve (arrow). **B**) A sagittal T2-weighted image showing a cervical cord lesion extending from C6 to T3 (arrow). **C**) An axial T2-weighted image showed no abnormal findings. **D**) A sagittal T2-weighted image showing spinal cord atrophy and a lesion extending from C3 to T2 (arrow).

38°C. She then developed a relapse with quadriparesis and urinary incontinence. On physical examination, her temperature was 38.1°C, her pulse rate was 87 beats/min, her blood pressure was 130/80 mm Hg, and respiration was 18 breaths/min. There were no signs of dehydration. Muscular tension was slightly decreased, and muscle strength was 3/5 in arms and 0/5 in her legs. Both Babinski and Chaddock signs were positive. Sensation was bilaterally diminished below the level of C8. A repeat brain MRI did not reveal any abnormalities (**Figure 1C**). A cervical MRI showed the spinal cord atrophying and a lesion extending from C3 to T2 (**Figure 1D**). The serum AQP4 antibody titer was positive (titer 1:320) as determined by a cell-based assay. Laboratory investigations demonstrated significant hyponatremia to a nadir of 113 mmol/L (**Table 1**). Markers of autoimmune diseases, such as antinuclear antibodies (ANA), extractable nuclear antigen (ENA), anti-dsDNA antibodies, and anti-neutrophilic cytoplasmic antibodies (ANCA) were all negative. Epstein-Barr virus antibody, syphilis serology, and HIV antibodies were negative. Blood, sputum, and urine cultures were negative. Results of paraneoplastic tests were all normal. The patient's anti-TB test was negative, and her adenosine deaminase was within the normal range. Thyroid functions, and female hormones were within normal limits. Plasma

**Table 1 -** Laboratory data obtained during the patient's last hospital admission.

| Laboratory test (reference range) | Admission | Day 3 | Day 7 | Day 18 |
|---|---|---|---|---|
| *Routine blood tests* | | | | |
| WBC (4-10 x $10^9$ WBC/L) | 5.61 | 6.02 | 6.52 | 7.47 |
| % Neutrophils (50-75) | 65.9 | 62.7 | 56.8 | 59.2 |
| % Lymphocytes (20-40) | 35.6 | 30.0 | 32.1 | 24.8 |
| % Eosinophil (0-5) | 0.20↓ | 0.6 | 0.5 | 0.7 |
| RBC (3.5-5.5 x $10^{12}$ RBC/L) | 3.50 | 3.21 | 3.26 | 3.29 |
| HGB (110-160 g/L) | 123 | 112 | 115 | 117 |
| *Serum parameters* | | | | |
| BUN (2.1-8.2 mmol/l) | 1.48↓ | 1.76↓ | 2.05↓ | 2.2 |
| Uric acid (149-458 µmol/L) | 63↓ | 95↓ | 96↓ | 76↓ |
| Glucose (3.36-6.16 mmol/l) | 6.41 | 4.86 | 4.69 | 5.12 |
| Sodium (135-145 mmol/l) | 113↓ | 128↓ | 125↓ | 135 |
| Potassium (3.5-5.5 mmol/l) | 3.2 | 3.6 | 3.7 | 3.5 |
| Chloride (96-106 mmol/l) | 87.5 | 94.2 | 93.2 | 98.4 |
| Phosphorus (0.81-1.78 mmol/l) | 1.51 | 1.68 | 1.73 | 1.65 |
| Magnesium (1.7-2.9 mg/dl) | 1.6 | 1.27 | 1.79 | 1.73 |
| Calcium (2.12-2.88 mmol/l) | 2.01 | 2.09 | 1.97 | 2.0 |
| *Urine parameters* | | | | |
| Urinary WBC | 25/HP | 0 | 0 | 0 |
| Sodium (130-260 mmol/l) | 334 | 300 | 280 | 265 |
| Potassium (25-100 mmol/l) | 27 | 26.8 | 31.2 | 30.5 |
| SG (1.015-1.025) | 1.010 | 1.010 | 1.010 | 1.015 |
| Urine Osm/Blood Osm (mosm/L) | 560/271 | 420/241 | 400/268 | 302/305 |
| *Arterial blood gases* | | | | |
| pH | 7.465 | 7.461 | 7.446 | |
| P (mm Hg) $CO_2$ | 35.6 | 34.8 | 35 | |
| P (mm Hg) $O_2$ | 69.4 | 80.1 | 91.3 | |

WBC - white blood cell, RBC - red blood cell, HGB - hemoglobin, BUN - Blood Urea Nitrogen, SG - specific gravity, OSM - osmotic pressure, ↓ - below reference range

renin activity and plasma aldosterone levels were normal. Repeat CSF revealed increased protein (51 mg/dl), and myelin basic protein (1.64 nmol/L, normal range ≤0.55). The CSF oligoclonal IgG was again negative. Her WBC counts and glucose level was normal. Examination of the CSF for infectious agents, including bacteria, cryptococci, fungi, tuberculosis, and viruses were all negative. The chest x-ray, chest CT, cardiac ultrasound, and abdominal ultrasound were all normal.

Upon admission, initial diagnoses of acute bronchitis and recurrent NMO were made. After abatement of her fever and symptomatic therapy, she had a normal body temperature. She was treated with methylprednisolone one g daily for 5 days followed by a reducing course of the drug. She also received intravenous immunoglobulin 0.4 g/kg/day for 5 days along with azathioprine. She continued to have hyponatremia, and was finally diagnosed with SIADH. Hypertonic saline (10%) was administered, and her daily water intake was restricted to 600 ml. Two weeks later, her neurological status was slightly improved and her serum sodium was normal.

**Discussion.** Lotze et al[5] reported the case of a 15-year-old Caucasian girl with AQP4 antibody positive NMO who had symptomatic hyponatremia caused by SIADH. While we report an adult case of an AQP4 antibody positive NMO patient with SIADH. She had repeated episodes of optic neuritis and myelitis, contiguous spinal cord lesions extending over 3 vertebral segments, and AQP4 antibody seropositive status, fulfilling the diagnostic criteria for NMO.[6] She also presented with hypotonic hyponatremia, natriuresis, and urine osmolality in excess of plasma osmolality. Her renal and adrenal functions were normal. In addition, she did not show any evidence of edema, dehydration, heart failure, or liver cirrhosis. She was diagnosed with SIADH according to the criteria proposed by Schwartz and Bartter.[7] Moreover, this diagnosis was supported by the presence of hypouricemia (serum uric acid levels 63 mg/dl) and decreased blood urea nitrogen. Low levels of uric acid are often seen in SIADH (70% of patients).[8] Other diseases that triggered the patient's hyponatremia were ruled out. She did not show any evidence of dehydration, and had normal hematocrit and plasma albumin concentrations after water restriction was initiated. These signs excluded the diagnosis of cerebral salt wasting syndrome. Normal renal function and plasma aldosterone levels ruled out salt-losing nephritis. Normal female hormone levels ruled out a glucocorticoid deficiency. In addition, agents such as thiazide diuretics, tricyclic antidepressants, and carbamazepine, which commonly cause SIADH, were not administered.[9]

The mechanisms of SIADH associated with NMO have not been well defined. The SIADH is a syndrome caused by an excessive secretion of antidiuretic hormone (ADH) or ADH-like substances.[7] Dysfunction of the hypothalamic-pituitary axis, which plays a central role in the regulation of ADH secretion, is responsible for SIADH. In our case, SIADH occurred simultaneously with exacerbation of neurological symptoms, and the AQP4 antibody was positive. The immune attack on AQP4 may secondarily affect the supraoptic and paraventricular nucleus of the hypothalamus, causing ADH leakage, which could then have triggered the SIADH. For example, Sakai et al[10] reported an autopsied case of SIADH associated with multiple sclerosis, and showed loss of neuronal cells of the supraoptic nuclei. Lotze et al[5] reported the case of a 15-year-old Caucasian girl with NMO who had symptomatic hyponatremia caused by SIADH. A brain MRI demonstrated increased T2 signal intensity in the hypothalamus.[5] Viegas et al[11] described a patient who presented with weight loss, vomiting, and behavioral changes. Hypothalamic lesions were confirmed by imaging and biopsy. However, our patient's MRI of the hypothalamus did not show any abnormal lesions. We speculate that there might have been damage to the tiny connective fibers of the hypothalamus, which could not be detected by MRI. Confirming that this is a possibility, Petravic et al[4] reported a NMO patient with hyperphagia, obesity, and amenorrhea due to hypothalamic dysfunction who did not have any brain involvement.

Besides SIADH, the association of other endocrinopathies, such as amenorrhea, and galactorrhea with NMO have also been described. In 1997, a special group of NMO cases associated with endocrinopathies was first described by Vernant et al.[12] These patients were characterized by rapid evolution to blindness and paraplegia, spinal cord involvement (cavitations with syringomyeloid sensory disturbance), normal brain MRI, and an association with hypothalamus-pituitary dysfunction, called "recurrent optic neuromyelitis with endocrinopathies." Six patients from Brazil, one from China, and one from Europe were reported subsequently.[3,4,13] In our patient, several characteristics were similar to this "recurrent optic neuromyelitis with endocrinopathies," although more studies are needed to define this disorder as a new syndrome.

In conclusion, AQP4 antibody positive NMO can be related to SIADH. Early recognition of the syndrome with NMO may provide therapeutic benefits.

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