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Case Report

Autonomic Dysregulation, Cognitive Impairment, and Symptoms of Psychosis as an Unusual Presentation in an Anti-Aquaporin 4-Positive Patient

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Keywords

Neuromyelitis optica · Anti-aquaporin 4 · Hypothalamus · Psychosis · Cognitive impairment · Vision problems · Autonomic dysregulation

Abstract

We present the unusual case of a patient with an aquaporin 4 antibody-seropositive neuromyelitis optica spectrum disorder who presented with autonomic dysregulation, cognitive impairment, and symptoms of psychosis. Only a few previous cases have been described with similar psychiatric symptoms. Brain MRI showed an abnormal hyperintense T2 signal of the hypothalamus and, to a lesser extent, a minor hyperintense signal of the right optic nerve. Her symptoms and MR abnormalities improved after high-dose methylprednisolone.

Background

Neuromyelitis optica (NMO; formerly known as Devic disease) is an inflammatory demyelinating disease of the central nervous system which is characterized by severe relapsing

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episodes of transverse myelitis and optic neuritis. In the early stages, other parts of the central nervous system are spared, but we now know that later in the course of the disease other parts of the brain can be involved. For a long time, NMO was considered as a specific variant of multiple sclerosis, but it can now be distinguished as a different disease entity by specific MRI findings and the detection of anti-aquaporin 4 antibodies (anti-AQP4) or IgG serum antibodies against the myelin oligodendrocyte glycoprotein [1, 2]. Anti-AQP4 antibodies are found in patients with classic NMO, Asian opticospinal multiple sclerosis, isolated longitudinally extensive transverse myelitis, isolated optic neuritis, and, in rare cases, isolated brainstem encephalitis. Anti-AQP4 antibodies are not detectable in multiple sclerosis and have a 76% sensitivity and 94–99% specificity for a NMO spectrum disorder (NMOSD) [3]. NMO is associated with substantial cognitive and psychiatric comorbidities [4].

Case Presentation

A 28-year-old woman was admitted to our hospital with short-term memory problems, confusion, incoherent and delusional thinking, and self-neglect since 2 weeks. There was also loss of appetite and she had lost 7 kg of weight in the last 2 months. She was of mixed European/African ethnicity, and her previous medical history mentioned an attention deficit hyperactivity disorder for which she used methylphenidate 10 mg daily. Her psychiatric history showed a short period of paranoid features when she was 20 years old, possibly induced by overuse of methylphenidate.

On physical examination there was a body temperature of 34.8°C, an RR of 95/57 mm Hg, and a pulse rate of 80 beats/min. She had symptoms of bradyphrenia, bradykinesia, and slowed, halting speech and was disorientated in time and place. The Mini-Mental State Examination (MMSE) score was 26/30. The remaining physical and neurological examinations were unremarkable. Extensive ancillary testing was performed. Laboratory testing showed a leukocytosis of 27.7 × 10^9/L, a C-reactive protein level of 2.1 mg/L, and a mild hypernatremia of 148 mmol/L. Her thyroid function was normal and there were no vitamin deficiencies. A urine sample showed no abnormalities and drug testing was negative. HIV and lues screening was negative. A brain CT scan was normal.

She was admitted to our neurology ward, but after 2 days she was transferred to our medical psychiatric ward because of progressive confused behavior. The psychiatrist suspected a first psychotic episode with catatonic features; methylphenidate was discontinued and she was treated with lorazepam 0.5 mg twice a day. An antipsychotic drug was not yet started, because a somatic cause of her behavior had not been ruled out completely. She then developed hypothermia (32.6°C) and hypercapnia and was therefore transferred to the intensive care unit because of a suspected autonomic dysregulation. On the intensive care unit, her mental status deteriorated. A brain MRI showed an abnormal hyperintense signal on T2-weighted images and fluid-attenuated inversion recovery images of the hypothalamus (Fig. 1) and, to a lesser extent, of the right optic nerve, with enhancement after gadolinium. A cerebrospinal fluid examination revealed a mild pleocytosis of 60 cells/μL, a normal protein level of 0.45 g/L, and a normal glucose level of 3.6 mmol/L.

The differential diagnosis at that moment included hypothalamic encephalitis either caused by an autoimmune disorder or of viral origin, a systemic autoimmune disease, or a paraneoplastic disorder. Cerebrospinal fluid cultures showed no abnormalities and the paraneoplastic antibodies were negative. A CT scan of the thorax and abdomen showed no signs of sarcoidosis or an underlying malignancy. Anti-dsDNA and anti-Sm antibodies were

absent, ruling out systemic lupus erythematosus. Anti-Sjögren syndrome-related antigen B (anti-SSB) antibodies were positive, but in combination with a negative test for anti-SSA and normal findings at a lip biopsy, Sjögren syndrome was considered highly unlikely.

The patient was treated with intravenous methylprednisolone pulse therapy for 3 days, at 1,000 mg per day, which resulted in resolution of the hypothermia and hypercapnia. A second cerebrospinal fluid analysis showed an IgG index of 0.52 with oligoclonal bands. Considering all the normal results on testing and the prompt reaction to steroids, an NMOSD was considered and was confirmed by positive tests for serum anti-AQP4 antibody. After the 3-day course of intravenous methylprednisolone, we continued treatment with oral prednisolone at 30 mg twice a day and azathioprine at 50 mg twice a day. Because she developed apraxia and hypomanic features such as hypersexuality and overeating in combination with the preexisting cognitive and behavioral problems, she was retransferred to the medical psychiatric ward and treated with haloperidol at 2.5 mg and with lorazepam. Her MMSE score at that moment was 14/30. An ophthalmologist confirmed vision of 0.5/200 and 20/25, respectively, in the right and the left eye. On treatment with haloperidol and lorazepam, the hypomanic symptoms and delusional thinking subsided. After 6 weeks, she was discharged to a rehabilitation center with severe memory and visual problems. Oral prednisolone was continued in a 22-month tapering schedule; azathioprine was continued at 50 mg twice a day. After a couple of weeks in rehabilitation, she was again transferred to a psychiatric unit with a compulsive eating disorder and aggressive behavior probably due to a combination of treatment with prednisolone and a brain injury caused by the initial brain lesions. A repeat MRI scan 3 months later showed almost complete recovery of the hypothalamic lesions, and there were no signs of new disease activity.

Discussion

Our patient presented with bilateral hypothalamic lesions and concomitant optic neuritis as a first episode of an NMOSD. There are only a few cases describing patients with hypothalamic lesions as an initial symptom, all of them presenting with excessive daytime sleepiness as a first symptom. Our patient presented with cognitive impairment, autonomic failure, and symptoms of psychosis, but no sleep disturbances. Only 2 cases with symptoms of psychosis were described [5, 6]. Most of the NMOSD patients were young women between 20 and 45 years of age [7–11]. Remarkably, all patients were of Asian ethnicity, whereas our patient was of mixed Caucasian/Negroid origin. It is well described that NMO is more common in nonwhite populations, in contrast to the low incidence of multiple sclerosis in nonwhite persons [1]. All patients were treated with intravenous methylprednisolone, some followed by oral prednisolone, with variable outcomes: no symptoms at follow-up, relapses of sleepiness, and memory disturbances, as well as symptoms matching new brain or spinal cord lesions were reported [7–11].

Whereas in multiple sclerosis, spontaneous remission may have an equal effect to high-dose immunosuppressive medication on the long-term neurological outcome, in NMOSD repetitive episodes will lead to severe damage, and the current consensus is to treat every relapse to prevent severe long-term damage. The recommended treatment for an acute episode of NMO is high-dose methylprednisolone intravenously for 5 days followed by an oral steroid taper for 2–8 weeks depending on the severity of the attack. If high-dose corticosteroids have no or only a minimal effect, a plasma exchange is considered to be effective. Maintenance therapy is accomplished by azathioprine or other immunosuppressive medica-

tion [1]. White matter brain lesions are reported in up to 50–85% of patients with NMOSD, and 43–70% of these brain MRI abnormalities are reported at onset. Usually, the lesions are asymptomatic and most often located in areas with high AQP4 expression, such as the hypothalamus, but also subcortical and deep white matter lesions are common [1, 12].

A recent study by Gao et al. [13] investigated the presence of hypothalamic lesions in inflammatory diseases including NMOSD, multiple sclerosis, and acute disseminated encephalomyelitis, as well as in lupus, sarcoidosis, Behçet disease, CLIPPERS (chronic lymphocytic inflammation with pontocerebellar perivascular enhancement responsive to steroids), and hypertrophic pachymeningitis. In all, 172 of the 429 study subjects were AQP4 positive and met the criteria for NMOSD defined by Wingerchuk et al. [1] (which have recently been updated [14]). In 42 subjects (24.4%) with NMOSD there were hypothalamic lesions on T2-weighed MR images, of which 90% were bilateral; 10 out of 257 APQ4-negative subjects had hypothalamic lesions.

NMOSD is associated with other autoimmune disorders, especially connective tissue disorders like Sjögren syndrome and systemic lupus erythematosus. The exact relationship between NMOSD and other autoimmune disorders is not quite fully established, but there might be a link between AQP4 seropositivity and other connective tissue autoimmune disorders [1, 15]. Our patient had a positive anti-SSB serologic test, but a lip biopsy showed no signs of a coexisting Sjögren syndrome, and also additional tests for systemic lupus erythematosus were negative, which is why we treated her as a patient with an NMOSD. NMOSD is a severe disease with a variety of symptoms. Hypothalamic lesions are a common manifestation. Physicians should consider performing an MRI and lumbar puncture in young women presenting with hypothalamic symptoms or atypical psychosis. Early treatment with high-dose methylprednisolone is recommended to prevent severe long-term damage. Integrated neurological and psychiatric care for these patients is recommended.

Statement of Ethics

Informed consent was obtained from the patient.

Disclosure Statement

The authors declare no conflict of interest.

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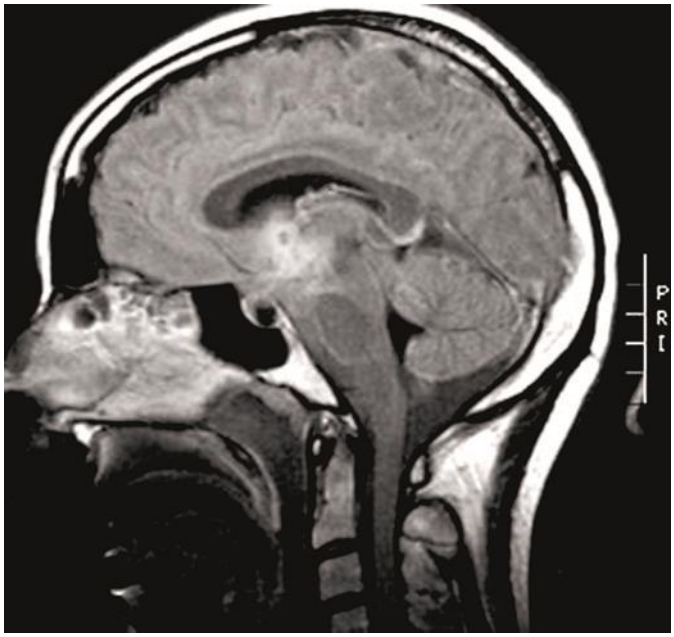

Fig. 1. Axial fluid-attenuated inversion recovery image showing a bilateral hyperintense signal in the hypothalamus.