Case Report

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Concomitant abducens and facial nerve palsies: A rare presentation in anti-aquaporin-4 antibody-positive neuromyelitis optica

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Abstract:

Over the past decade, the discovery of disease-specific aquaporin-4 antibodies has led to a better understanding of the diverse spectrum of disorders that are associated with neuromyelitis optica. Brainstem manifestations have been increasingly recognized in this disease. However, multiple cranial nerve palsies as an initial presentation of neuromyelitis optica are uncommon. We report a rare case of anti-aquaporin-4 antibody-positive neuromyelitis optica that presented with unilateral abducens and facial nerve palsies. Notably, this case did not involve the optic nerve or the spinal cord. Diagnosing neuromyelitis optica that presents as an isolated acute brainstem syndrome is challenging, but the outcome may be devastating if the diagnosis is delayed.

Keywords:

Acute brainstem syndrome, anti-aquaporin-4 antibody, concomitant facial and abducens nerve palsies, neuromyelitis optic

Introduction

Neuromyelitis optica is an inflammatory disorder caused by immune-mediated demyelination of the nervous system. Classically, the disease is characterized by optic neuritis and acute myelitis. Conventionally, neuromyelitis optica was not considered to involve the brain. However, the discovery of a serum immunoglobulin G antibody that selectively binds to aquaporin-4 has led to a broader understanding of the diverse spectrum of this disorder.[1] The accumulated evidence from the past decade has revealed that neuromyelitis optica might affect various regions of the brain, leading the disease to be described as neuromyelitis optica spectrum disorder.[2]

Brainstem syndromes have a higher prevalence in non-Caucasian populations. The most common manifestations are hiccups and vomiting.[3] The occurrence of multiple cranial nerve palsies in neuromyelitis optica is rare. Here, we describe a case of anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder that presented as abducens and facial nerve palsies. This unusual presentation posed a challenge for early diagnosis and disease management.

Case Report

A previously healthy 39-year-old Chinese woman presented with an acute onset of diplopia, oscillopsia, and facial weakness that had occurred on her left side during the previous week. Her visual acuity was affected by horizontal oscillopsia, and there were diplopia symptoms in her left gaze. There was no blurring of her vision, pain on ocular movement, field loss, or dyschromatopsia.

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Three weeks before the consultation, the patient had presented to a surgeon with persistent epigastric discomfort, dyspepsia, and hiccups. She underwent an esophagogastroduodenoscopy, and a *Campylobacter*-like organism test indicated that she had a *Helicobacter pylori* infection. The patient commenced an *H. pylori* eradication therapy that consisted of oral metronidazole at 400 mg and clarithromycin at 250 mg, administered twice daily for a week.

A week later, she developed intractable hiccups and frequent vomiting. Her condition deteriorated, and she developed new-onset symptoms of unsteady gait, diplopia, oscillopsia, and left-sided facial weakness [Figure 1].

The patient's best-corrected visual acuity was 20/20 OU. Her primary gaze was orthophoric. However, the left eye had limited abduction, and there were signs of multidirectional, horizontal gaze-evoked nystagmus. The pupillary reflex was normal in both eyes and devoid of any relative pupillary defect. The anterior and posterior segment examinations were normal. The visual field and color vision tests were within the normal ranges.

On systemic examination, the patient was comfortable and afebrile. Her vital signs were stable. Neurology assessment revealed that the patient had acute area postrema syndrome, appendicular ataxic gait, and left facial nerve palsy of the lower motor neuron type. The Romberg's test was positive. The other cranial nerves were intact.

There were no signs suggestive of acute myelitis noted. The patient's muscle strength and tone were normal, along with the reflexes in all four limbs. Her thermal sensation, soft touch, and proprioception were intact. No clonuses were observed, and the Babinski reflex was negative.

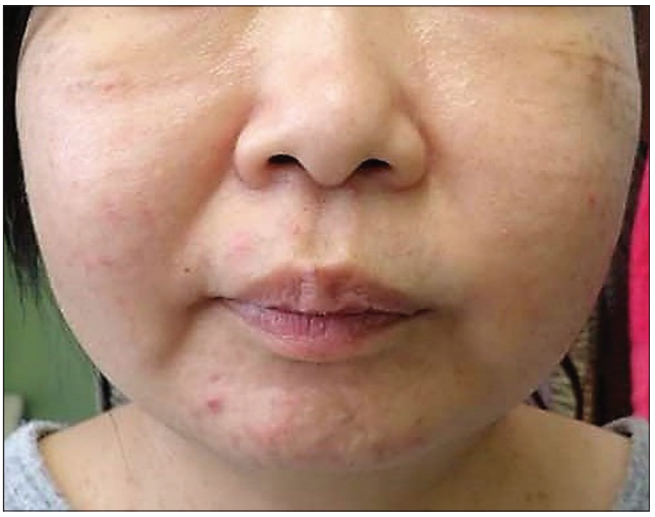

Figure 1: Loss of the left nasolabial fold

The patient's full blood count and renal profile were normal. An indirect immunoflourescence assay for serum anti-aquaporin-4 antibody was positive. The cerebrospinal fluid analysis showed the presence of 12 cells/μL (red blood cells + 1000) with elevated levels of total protein (483 mg/dL). The glucose cerebrospinal fluid-to-serum ratio was normal at 0.61. There was no oligoclonal band detected in the analysis.

Magnetic resonance imaging (MRI) of the brain and spinal cord showed an abnormal T2-weighted image, and fluid-attenuated inversion recovery images revealed hyperintense areas within the hypothalamus, the periaqueductal region, the caudal portion of the pons, and the left inferior cerebellar peduncle, as well as in the medulla oblongata at its central canal surrounding region and at the dorsal margin, including the area postrema [Figure 2a and b]. A marked abnormal leptomeningeal enhancement was also seen at the basal cistern. Neither the optic nerve nor the spinal cord showed any gadolinium enhancement.

Based on the clinical manifestations, radiological imaging, and laboratory results, the patient was diagnosed with a limited form of neuromyelitis optica spectrum disorder. She was treated with intravenous methylprednisolone therapy (1 g/day for 3 days), followed by oral prednisolone (1 mg/kg/day for 7 days). The medications were gradually tapered, with close monitoring for relapse and possible side effects.

The patient demonstrated remarkable clinical improvement after 2 weeks of medication. There was no diplopia, oscillopsia, hiccups, or vomiting during the follow-up visits. Her extraocular muscle movement had improved to full abduction on the left side. The lagophthalmos caused by the left facial palsy had also improved.

After 12 weeks of the treatment regimen, the patient presented with hiccups during a follow-up visit. At that

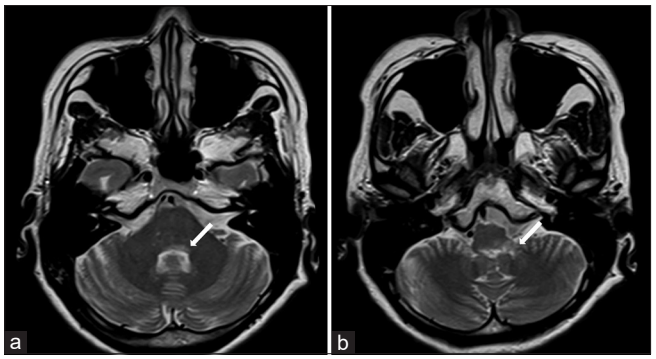

Figure 2: T2-weighted image of the magnetic resonance imaging showing abnormal signal changes at, (a) the left caudal portion of the pons (arrowed) and (b) the dorsal medulla and left cerebellar peduncle (arrowed)

point, she was on daily oral prednisolone of 7.5 mg and daily azathioprine of 100 mg (2 mg/kg/day). In view of the recurrent attack, she was prescribed a combination of daily oral prednisolone of 30 mg and daily oral azathioprine of 100 mg. Her symptoms improved after the administration of the revised treatment.

Six months after the initial attack, the patient remained asymptomatic with minimal residual left facial nerve palsy. The serum anti-aquaporin-4 antibody test was repeated, and the results were negative. She was on daily oral prednisolone of 15 mg and daily oral azathioprine of 100 mg and showed no indications of side effects related to the treatment.

Discussion

Acute attacks of optic neuritis and myelitis are the hallmarks of classically described neuromyelitis optica. The discovery of aquaporin-4 antibodies has led to a better understanding of the spectrum of the disease. The revised consensus criteria published in 2015 included the acute brainstem syndrome, acute area postrema syndrome, symptomatic narcolepsy syndrome, and symptomatic cerebral syndrome into the core diagnostic criteria of neuromyelitis optica spectrum disease.[4]

Our patient had a recent *H. pylori* infection that was preceded by an acute area postrema syndrome and an acute brainstem syndrome. These early symptoms were devoid of any optic neuritis or myelitis. The area postrema syndrome manifested as hiccups and severe vomiting. The acute brainstem syndrome manifested as left abducens and facial nerve palsies, along with nystagmus. These core criteria correlated with MRI findings that included lesions on the brainstem and at the caudal portion of the pons (the left facial colliculus). The pons' lesions involved the ipsilateral abducens nucleus, the facial nucleus, and the postrema area at the dorsal medulla.

Aquaporins are water channels that present on cell membranes mainly expressed on the foot processes of astrocytes and ependymal cells in the central nervous system. Highly expressed aquaporin-4 is located in the retina, optic nerve, spinal cord, hypothalamus, and cerebellum, as well as in the periventricular and periaqueductal regions. Low expression levels can be found in the cerebral cortex.

The pathogenesis of neuromyelitis optica involves the production of abnormal autoantibodies against aquaporin-4 expression, a protein that is expressed on astrocytic foot processes in the central nervous system. These autoantibodies mediate a complement-dependent necrosis of the astrocytes. This autoimmune inflammation causes neuronal demyelination and damage. The onset timing differences that occurred in our patient (between the area postrema syndrome and acute brainstem syndrome) were probably due to inflammation occurring at different anatomical locations. The area postrema is a circumventricular structure that is characterized by the presence of fenestrated capillaries and loosely apposed astrocytic processes. This unique vascular architecture may facilitate the entry of neuromyelitis optica-specific immunoglobulin G.[5]

Kremer *et al*. conducted a multicenter study of 258 patients with neuromyelitis optica spectrum disorder. Brainstem symptoms were observed in 81 (31.4%) patients, along with vomiting (33.7%) and hiccups (24%). Of the patients with brainstem symptoms, 67 (32.7%) patients were in the seropositive anti-aquaporin-4 antibody group, and 14 (26%) patients were in the seronegative group. Only 2.9% of the patients in the study had facial nerve palsies, and only 1.9% presented with ataxia.[3] To date, there are no other documented reports of concomitant abducens and facial nerve palsies as an early presentation of this disease.

Recent studies have suggested that *H. pylori* infection might trigger neuromyelitis optica,[6-8] and the infection seems to be a risk factor for the development of anti-aquaporin-4 antibodies. The inflammatory mediators that are induced by *H. pylori* infection, such as cytokines, chemokines, and oxidative stress, have been implicated in the disruption of the blood–brain barrier. This phenomenon may allow the aquaporin-4 antibodies to access the central nervous system.[9]

The Neuromyelitis Optica Study Group recommends azathioprine as the frontline therapy for long-term immunosuppression of neuromyelitis optica.[10] Because this immunosuppressant requires 3–6 months to become biologically active, it should initially be combined with a high-dose oral steroid therapy (1 mg/kg of body weight/day) followed by a slow taper over 1 year. This combination therapy has been shown to effectively reduce the annual relapse rate of the disease and to improve the expanded disability status scale score.[10,11] Our patient's azathioprine dosage regimen was 2 mg/kg/day because the prevailing studies indicated that doses < 2 mg/kg/day were associated with more frequent attacks than higher azathioprine doses, especially during the first year of the disease.[12]

Multiple studies have shown that effective immunosuppressive treatment results in a significant reduction in anti-aquaporin-4 antibody titers.[11,13,14] However, increases in anti-aquaporin-4 antibody titers do not always correlate with a clinical relapse. Consequently, anti-aquaporin-4 antibody levels may be useful indicators

for the effectiveness of the immunosuppressive treatment, but antibody levels cannot be relied on to predict clinical relapse. Additional factors, such as the permeability of the blood–brain barrier, complement activation, and the influence of antigen-specific T-cells, should be considered. Interestingly, it is not uncommon for a patient with a seropositive anti-aquaporin-4 antibody response to convert to seronegative during the remission stage. Kim *et al*. revealed that 55% of 38 seropositive patients who underwent immunosuppressive therapy had a seronegative conversion.[13]

The majority of documented neuromyelitis optica cases have involved relapses. Optic neuritis and transverse myelitis in neuromyelitis optica attacks tend to be more severe. The disabilities associated with the disease are generally attack related and most occur during the progressive phase of the illness.[15] Brainstem symptoms are reversible in most cases, but the sequelae may persist, especially in patients with hearing loss and oculomotor dysfunction. Some patients may endure long-term oscillopsia or nystagmus. The risk of these complications emphasizes the importance of early treatment.[3]

Conclusion

The acute onset of concomitant abducens and facial nerve palsies may indicate a variant of neuromyelitis optica spectrum disorder. Prompt diagnosis and early treatment are critical for achieving good clinical outcomes. It is important to screen for *H. pylori* infection in patients with seropositive anti-aquaporin-4 antibodies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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