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LETTER TO THE EDITOR

Neuromyelitis optica spectrum disorder complicated with Sjögren's syndrome: first pediatric case responsive to mycophenolate mofetil treatment

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Dear Editor,

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease of the central nervous system affecting patients in their 40 s and 50 s [1]. Primary Sjögren's syndrome (pSS) is another autoimmune disorder which is sometimes found in association with NMOSD in adult patients. However, it is rare for NMOSD and pSS to coexist in children. Here we describe a 14-year-old girl with pSS who developed anti-aquaporin-4 immunoglobulin G (AQP4-IgG) positive NMOSD with typical lesions in the corpus callosum responsive to mycophenolate mofetil treatment.

Case report

A 14-year-old girl complained of new-onset dizziness and headache for 10 days. About 8 months ago, she was diagnosed as pSS based on the oral sicca symptoms, rampant caries, anti-Sjögren's syndrome-related antigen A (SSA)/Ro antibody positivity and a decreased unstimulated salivary flow rate of 0.087 mL/min. No treatment was given at that time. She suffered from bilateral acute vision loss (visual acuity, limited to a finger count at 5 cm on the right eye and light perception on the left eye) half a year ago, which was diagnosed as bilateral optic neuritis by the ophthalmologist. Symptoms improved (visual acuity, limited to a finger count at 30 cm on the right eye and 20/40 on the left eye) with a daily 500 mg intravenous (IV) methylprednisolone for 5 days and the subsequent oral prednisone was ceased quickly. However, her vision loss had not fully recovered. Neurologic examination of this time showed impaired binocular vision, brisk reflexes, and positive Babinski sign. Routine laboratory examinations such as thyroid function, biochemical test and blood routine examination were normal except for immunologic tests, which showed anti-SS-related antigen A antibodies (+++), anti-SS-related antigen B antibodies (+++) and anti-Ro52 antibodies (+++). Cerebrospinal fluid analysis was unremarkable except for an elevated protein (75.5 mg/dL). Oligoclonal band was negative. Brain magnetic resonance imaging revealed diffuse hyperintensity (Fig. 1a, b) in the corpus callosum without contrast enhancement (Fig. 1c), creating a "marbled pattern". The complete thickness of genu and splenium hyperintensity revealed an "arch bridge pattern" with periependymal involvement (Fig. 1d). Serum AQP4-IgG was positive and myelin oligodendrocyte glycoprotein-IgG was negative (both by cell-based assay).

The patient was diagnosed as NMOSD complicated with pSS and was treated with a daily 500 mg IV methylprednisolone for 5 days followed by an oral tapering. Upon treatment, her symptoms improved significantly. Next, the regimen of secondary prevention was discussed in a multidisciplinary panel including neurologists and rheumatologists. Though rituximab or azathioprine was suggested, the patient's parents refused both regimen due to financial issues

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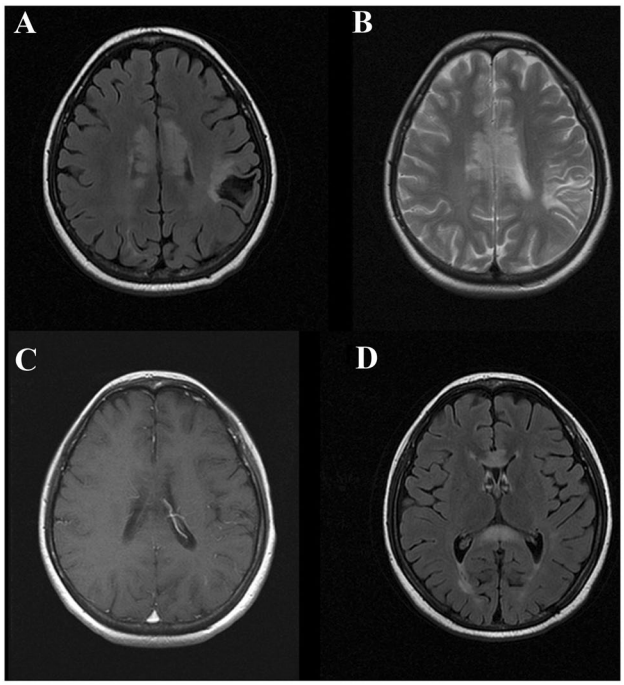

Fig. 1 Callosal lesions with "arch bridge" and "marbled patterns". Callosal hyperintensity in FLAIR (**a**) and T2-weighted (**b**) showed a "marbled pattern", without contrast enhancement (**c**). The complete thickness of genu and splenium hyperintensity revealed an "arch bridge pattern" with periependymal involvement on FLAIR (**d**). Note there existed encephalomalacia in the left parietal lobe but with no clinical history (**a**). *FLAIR* fluid-attenuated inversion recovery

and concerns regarding medication compliance. Ultimately, cyclophosphamide was given every month to prevent future attacks apart from prednisone. In the first-year follow-up, despite continuous immunosuppressive therapy, she suffered from two neurological events consistent with optic neuritis relapses, though lesions were not detected on orbital MRI. Therefore, we changed her immunosuppression treatment to mycophenolate mofetil (1000 mg/d, twice daily) and prednisone. At the most recent follow-up half a year ago, the patient was on a low-dose oral prednisone of 15 mg per day and no neurological relapses were reported.

Discussion

There were no special diagnostic criteria of pSS for pediatric patients. The diagnosis of pSS was made based on the oral sicca symptoms, anti-SSA/Ro antibody positivity and an unstimulated salivary flow rate of ≤ 0.1 mL/min, according to the 2016 American College of Rheumatology/European League Against Rheumatism criteria [2]. According to the 2015 diagnostic criteria of the International Panel for NMO Diagnosis also applicable for pediatric patients [3], the diagnosis of NMOSD was reached given the history of bilateral optic neuritis, radiographic lesions spanning the brain as well as a positive AQP4-IgG.

In patients with pSS and NMOSD, it is unclear whether NMOSD is only the neurological manifestation of pSS, or that the two diseases coexist as independent entities. Studies based on adult patients showed that transverse myelitis is a relatively common neurological manifestation of pSS apart from optic neuritis. However, recent studies consider NMOSD as an independent disease coexisting with pSS. In 109 pSS patients, Birnbaum et al. found that AQP4-IgG was detected exclusively in pSS patients with NMOSD [4]. Pathological results of a patient diagnosed of pSS and NMOSD showed active demyelination with edematous changes rather than vasculitis [5], which further supported the assumption that these two diseases coexist as independent entities.

Previous studies showed that pediatric patients of NMOSD presented with symptomatic brain lesions more commonly than adult patients [6]. The pediatric NMOSD-related brain involvement is mainly characterized by subcortical white matter lesions and lesions located in the areas of high AQP4 expression such as periependymal areas of the fourth and third ventricles, which is similar to that of adult patients. Besides, Bulut et al. retrospectively examined initial brain MRI of pediatric NMOSD and acute disseminated encephalomyelitis (ADEM) patients, and found a considerable overlap in brain MRI findings, making it difficult to differentiate pediatric NMOSD from ADEM [7]. Testing for AQP4-IgG can assist pediatricians in making an early and correct diagnosis. However, lesions of corpus callosum only accounted for about 5% of NMOSD children with MRI brain abnormalities [8]. Corpus callosum involvement may occur in various demyelinating diseases, especially NMOSD and multiple sclerosis. The acute callosal lesions in NMOSD show unique arch bridge and marbled patterns, which serves as a differentiating feature of NMOSD. To our knowledge, the pattern of callosal lesions in this patient has never been reported in children with NMOSD and pSS.

Treatment of NMOSD is mainly composed of corticosteroids for the acute phase and immunosuppressive agents to prevent future attacks. The immunosuppressive agents for relapse prevention therapy include azathioprine, rituximab, mycophenolate mofetil and cyclophosphamide in adults. Shahmohammadi et al. reviewed recent studies and drew a conclusion that patients of NMOSD associated with pSS had a higher severity of disease than patients with NMOSD alone [9]. However, whether these patients, especially in children, need different therapeutic decisions is under discussion. Some scholars suggested rituximab as a considerable preventive treatment in this situation, as rituximab was proven to be effective in treating both pSS and NMOSD [10]. Additionally, recent reports demonstrated that patients with NMOSD and pSS responded well to tocilizumab, a humanized monoclonal antibody to the interleukin-6 receptor [11].

To our knowledge, our patient was the first pediatric case with NMOSD and pSS responsive to a combination therapy of mycophenolate mofetil and prednisone. Further studies are required to confirm the effectiveness of mycophenolate mofetil in pediatric patients with NMOSD and pSS.

In conclusion, our patient with pSS broadens the phenotypic and radiologic spectrum of pediatric NNOSD. Investigation for AQP4-IgG in pSS patients with clinical findings suggestive of NMOSD aids in the early diagnosis and treatment of the disease.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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