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Neuromyelitis optica in a young child with positive serum autoantibody

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Abstract

Relapsing neuromyelitis optica is rare in children. The identification of highly specific serum autoantibody marker (neuromyelitis optica –immunoglobulin G) differentiates neuromyelitis optica from other demyelinating disorders particularly in clinically challenging cases. We present a child with multiple episodes of transverse myelitis and optic neuritis with positive neuromyelitis optica-immunoglobulin G titers consistent with a diagnosis of relapsing neuromyelitis optica. Serial titers of neuromyelitis optica-immunoglobulin G then normalized during remission.

Keywords

NMO; immunoglobulin G; myelitis; optic neuritis

Introduction

Neuromyelitis optica (also called Devic's disease) is an inflammatory, demyelinating disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Optic neuritis and myelitis can occur simultaneously or consecutively. Neuromyelitis optica may have a monophasic or a relapsing course and attacks may be separated by months or years [1]. It has been debated whether neuromyelitis optica is a variant of multiple sclerosis or a separate disease. Neuromyelitis optica is now recognized as a distinct entity. Large clinical series in adult patients reveal that most patients with neuromyelitis optica have longitudinally extensive transverse myelitis defined by a magnetic resonance imaging (MRI) lesion extending over three or more vertebral segments, which is exceedingly rare in multiple sclerosis [2]. Unlike multiple sclerosis, neuromyelitis optica is not usually associated with brain lesions at disease onset, and although brain lesions may develop over time, they mostly are non-specific and remain asymptomatic [3,4]. In contrast to multiple sclerosis, oligoclonal bands are not commonly found in the cerebrospinal fluid of patients with neuromyelitis optica [2]. Furthermore, the discovery of the serum autoantibody neuromyelitis optica - immunoglobulin G, distinguishes neuromyelitis optica from other inflammatory demyelinating disorders [5]. We present a child with relapsing neuromyelitis optica confirmed by positive neuromyelitis optica - immunoglobulin G antibody and documented changes in titers with her disease course occurring at the youngest age of onset reported in the English literature.

Case Report

A 3 year and 11 month old previously healthy girl presented with acute onset of bilateral leg weakness and urinary and bowel incontinence. She had an upper respiratory infection and papular rash during the preceding week. On examination, she was unable to lift her legs against gravity. Lower extremity deep tendon reflexes were decreased and plantar responses were extensor bilaterally. Sensory examination was normal. Brain MRI was normal; however, spine MRI demonstrated lesions consistent with longitudinally extensive transverse myelitis (Figure 1). Cerebrospinal fluid showed 32 white blood cells (89% lymphocytes), 365 red blood cells, glucose of 58 mg/dl and protein of 54 mg/dl. Immunoglobulin G index was normal, but the sample was not sufficient for oligoclonal band testing. Investigations for Epstein Barr virus, Herpes Zoster, Lyme disease and other infectious agents included in the meningoencephalitis panel were negative. Antinuclear antibodies, antiphospholipid antibodies, anti-neutrophilic cytoplasmic antibodies, and antistreptolysin O were all negative. Angiotensin converting enzyme and complement levels were normal and erythrocyte sedimentation rate was 42. The patient was treated with intravenous methyl prednisolone, followed by a tapering dose of oral prednisone. She recovered within two months. Follow-up MRIs of the spine showed improvement of the lesions with mild residual signal changes and no contrast enhancement.

Eleven months after the first event, the patient developed left hand paresthesias following a prodromal viral illness. She had decreased strength and deep tendon reflexes of the left arm, but otherwise had a normal examination, including visual acuity. MRI of the spine showed signal abnormalities extending from the lower medulla to C4 with minimal enhancement. Cerebrospinal fluid studies showed pleocytosis with lymphocyte predominance, immunoglobulin G index of 0.57 (upper limit 0.7) and no oligoclonal bands were found by isoelectric focusing. High dose intravenous methyl prednisolone was administered and all symptoms resolved quickly. The patient was treated with monthly intravenous immunoglobulin infusion for preventive immunotherapy, but was discontinued after an anaphylactic reaction with the third dose. One year later, brain and spine MRIs were unremarkable except for a small residual T2 signal abnormality at C1.

Four years after the second episode, the patient presented with left optic neuritis preceded again by an upper respiratory infection. She had only light perception in the left eye along with a left afferent pupillary defect and left papillitis. The right eye was normal as well as the remainder of the neurological examination. MRI of the spine demonstrated enhancing lesions consistent with longitudinally extending transverse myelitis. The brain MRI showed asymptomatic lesions in the left frontal subcortical white matter and right cerebral peduncle (Figure 2). At this point, neuromyelitis optica –immunoglobulin G testing was available and was highly positive at 1:1920 (normal < 1:120). The child was treated with intravenous methyl prednisolone and oral steroids tapered over three months. Visual acuity returned to normal and repeat neuromyelitis optica titer was 1:120 at two months follow up. Three months later, follow up spine MRI showed improvement and the brain MRI was normal.

Four months after the episode of left optic neuritis and one month after steroids were discontinued, the patient developed right optic neuritis. An upper respiratory infection preceded this presentation. The only finding on her examination was decreased visual acuity of right eye (20/400). Her brain MRI did not show any new lesions. She again responded to intravenous methyl prednisolone and was maintained on a combination of prednisone and azathioprine for one year. Neuromyelitis optica -immunoglobulin G titer at 3 months from this last relapse was negative.

She is currently only on azathioprine and has been relapse-free for 20 months. Her neurological examination, visual acuity, ocular coherence tomography, and urodynamic studies remain normal seven years after the disease onset.

Discussion

The rarity of neuromyelitis optica is underscored by the reported prevalence in children with demyelinating diseases between 3.2- 8.5% [6]. Our demyelinating disease cohort in Pittsburgh finds a consistent prevalence of 4% (4 out of 102 patients) and to date includes only this index patient with relapsing neuromyelitis optica with documented presence of neuromyelitis optica -immunoglobulin G autoantibody. The youngest case of neuromyelitis optica previously reported in the literature was a 23 month-old child with a single episode and the neuromyelitis optica -immunoglobulin status was not reported [7]. Therefore, our case is an important contribution as we report a very young child with relapsing neuromyelitis optica with positive neuromyelitis optica -immunoglobulin G titers documented during her disease course.

The neuromyelitis optica-immunoglobulin G autoantibody reacts specifically with aquaporin 4, a water channel molecule that is now utilized as a clinical marker and promises substantial understanding of the pathogenesis of neuromyelitis optica [2,5]. The presence of neuromyelitis optica-immunoglobulin G is included as a supportive criterion of the revised current diagnostic criteria by the Mayo Clinic group [6]. Since its discovery in 2004, several studies have shown the correlation of neuromyelitis optica- immunoglobulin G seropositivity and relapsing neuromyelitis optica [2]. Recently, Banwell et al. reported neuromyelitis optica-immunoglobulin G seroprevalance in childhood inflammatory demyelinating disorders and it was found in 78 % of children with relapsing neuromyelitis optica versus 12.5% in monophasic cases [6].

Our patient meets all the absolute and supportive diagnostic criteria for adult neuromyelitis optica proposed by Wingerchuk et al [1,8]. Similar criteria have been accepted by the Pediatric Multiple Sclerosis Study Group [9]. Initially, our patient had a normal MRI, but developed clinically silent brain lesions four years after the index event. The radiological findings of our case are consistent with other pediatric cases demonstrating brainstem, hypothalamus, corpus callosum, and cerebral lesions [3,6,10-11]. Particularly in young children with relapsing disease and central lesions, multiple sclerosis may be a diagnostic consideration. Our patient never developed symptoms implicating other CNS regions outside the optic nerves and spinal cord and the brain lesions were transient. More importantly, no neuromyelitis optica -immunoglobulin G titers have been identified in cases of pediatric relapsing remitting multiple sclerosis [6].

The presence of longitudinally extensive transverse myelitis has been suggested as a differentiating marker between neuromyelitis optica and multiple sclerosis by adult studies, but in pediatric cases, longitudinally extensive transverse myelitis has been observed in 14 % of MS patients [6]. Interestingly, our patient had two episodes of longitudinally extensive transverse myelitis only during the first four years of her disease and then developed optic neuritis. In cases initially presenting with only optic neuritis, the differential diagnosis includes various infectious and autoimmune disorders. Inflammatory demyelinating optic neuritis can be seen in isolation with a monophasic course, or can be associated with acute disseminated encephalomyelitis, multiple sclerosis or neuromyelitis optica. In cases of recurrent optic neuritis and recurrent myelitis, neuromyelitis optica-immunoglobulin G titer should be obtained as seropositivity has been reported in these groups [6]. Clinical relapses in the pediatric population are documented less frequently in children with neuromyelitis optica [6, 12], compared to a significantly higher rate in adult case series [2]. The Banwell study reported

a 53% relapse rate in children with neuromyelitis optica and no children were reported with relapses by Jeffrey et al, while the adult relapse rate is reported to be 80-90% [2].

The distinction between relapsing neuromyelitis optica and multiple sclerosis is important for planning long term preventive immunotherapy. It appears that interferons and glatiramer acetate are not as effective as prophylaxis for relapsing neuromyelitis optica as they are for multiple sclerosis [13]. At this time, there is no established protocol for long term preventive immunotherapy for relapsing neuromyelitis optica [2]. Long term combination treatment with prednisone and azathioprine was reported to be beneficial in a small adult series [14] and in the pediatric literature, there are only several single case studies using different agents [10-11,15]. Among the recent cases described in children, Domingues et al describes a 10 year boy with neuromyelitis optica associated with extensive cerebral white matter involvement who continued to relapse until he was maintained on a combination of prednisone, mitoxantrone and glatiramer acetate [10]. Another child, reported by Milani et al, with multiple relapses and a severe outcome also has striking abnormalities on brain MRI [11]. The patient was initially treated with steroids and intravenous immunoglobulin and after the fourth episode with cyclophosphamide, but then relapsed. Azathioprine was then started and the patient remained stable with resultant paraparesis and a severe visual impairment. Neither case documented the presence of the neuromyelitis optica autoantibody and whether these cases represent a broadening spectrum of neuromyelitis optica with acute disseminated encephalomyelitis-like lesions or multiple sclerosis remains controversial. These solitary cases underscore the difficulties of the diagnosis in relapsing inflammatory demyelinating disorders with overlap features in children and the potential importance of biomarkers. In our case study, the patient appears to have responded well to the combination of azathioprine and prednisone followed by azathioprine alone, and has demonstrated the normalization of the neuromyelitis optica –immunoglobulin G titer during her current clinical remission. In a recent study, anti-aquaporin 4 antibodies were observed to be low in three adult patients during the relapse-free periods under immunosuppressive therapy [16]. It is the subject of further studies whether these autoantibody titers correlate with disease severity, relapse rate or favorable response to therapy. Larger pediatric case series need to be conducted to evaluate the management issues in conjunction with clinical presentations, MRI findings, and response to therapies.

References

1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;53:1107–14. [PubMed: 10496275]
2. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol* 2007;6:805–15. [PubMed: 17706564]
3. Pittock SJ, Lennon VA, Krecke K, Wingerchuk DM, Lucchinetti CF, Weinshenker BG. Brain abnormalities in neuromyelitis optica. *Arch Neurol* 2006;63:390–6. [PubMed: 16533966]
4. Ghezzi A, Bergamaschi R, Martinelli V, Trojano M, Merelli E, Mancardi L, Gallo P, Filippi M, Zaffaroni M, Comi G. Clinical characteristics, course and prognosis of relapsing Devic's Neuromyelitis Optica. *J Neurol* 2004;251:47–52. [PubMed: 14999489]
5. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;364:2106–12. [PubMed: 15589308]
6. Banwell B, Tenenbaum S, Lennon VA, Ursell E, Kennedy J, Bar-Or A, Weinshenker BG, Lucchinetti CF, Pittock SJ. Neuromyelitis optica-Immunoglobulin in childhood inflammatory demyelinating CNS disorders. *Neurology* 2008;70:344–52. [PubMed: 18094334]
7. Yuksel D, Senbil N, Yilmaz D, Yavuz Gurer YK. Devic's neuromyelitis optica in an infant case. *J Child Neurol* 2007;22:1143–6. [PubMed: 17890418]
8. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485–9. [PubMed: 16717206]

9. Krupp LB, Banwell B, Tenenbaum S, International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007;68:S7–12. [PubMed: 17438241]
10. Domingues RB, Kuster GW, Lanes F, Callegaro D. Recurrent neuromyelitis optica with diffuse central nervous system involvement: case report. *Arq Neuropsiquiatr* 2004;62:543–6. [PubMed: 15273861]
11. Milani N, Zibordi F, Erbetta A, Pollo B, Angelini L. Neuromyelitis optica in a child with atypical onset and severe outcome. *Neuropediatrics* 2004;35:198–201. [PubMed: 15248104]
12. Jeffrey AR, Buncic JR. Pediatric Devic's neuromyelitis optica. *J Pediatr Ophthalmol Strabismus* 1996;33:223–9. [PubMed: 8880614]
13. Mandler RN. Neuromyelitis optica - Devic's syndrome, update. *Autoimmun Rev* 2006;5:537–43. [PubMed: 17027889]
14. Mandler RN, Waseem A, Dencoff JE. Devic's neuromyelitis optica: A prospective study of seven patients treated with prednisone and azathioprine. *Neurology* 1998;51:219–1220.
15. Hudson LA, Bernard TJ, Tseng BS, Miller BR, Corboy JR. Neuromyelitis optica immunoglobulin G in a child. *Pediatric Neurology* 2006;35:370–2. [PubMed: 17074612]
16. Takahashi T, Fujihara K, Nakashima I, Misu T, Miyazawa I, Nakamura M, Watanabe S, Shiga Y, Kanaoka C, Fujimori J, Sato S, Itoyama Y. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain* 2007;130:1235–1243. [PubMed: 17449477]

Figure 1.

First episode; sagittal T2-weighted (TR/TE : 3500/101 ms) cervical spine magnetic resonance imaging revealed increased signal abnormality from C2 - C6 consistent with longitudinally extensive transverse myelitis. There was also increased signal from mid T1 through mid T3 level which was enhanced with gadolinium.

Figure 2. Third episode; A) Coronal T2-weighted FLAIR (TR/TE: 10002/169 ms) and B) Axial T2-weighted image (TR/TE: 4000/97 ms) showed signal abnormality in the lateral aspect of the right peduncle, midbrain.