CASE REPORT

Longitudinal Extensive Transverse Myelitis: A Diagnostic and Therapeutic Challenge

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Abstract

Neuromyelitis optica spectrum disorders are inflammatory disorders of the central nervous system characterized by immune-mediated demyelination and axonal damage predominantly targeting the optic nerves and spinal cord.

We report the case of an 11 year-old boy, admitted with suspected viral meningitis. He developed bladder dysfunction and progressive ascendant sensory loss 24 hours after admission. The brain and spinal cord magnetic resonance showed extensive myelitis. Broad-spectrum antibiotics and immunoglobulin were started. Neurologic symptoms continued to progress and fundoscopy showed bilateral optic papillitis. Magnetic resonance on the eighth day showed the progression of the lesions and the involvement of the optic nerve, suggesting neuromyelitis optica spectrum disorder. High dose corticoids followed by plasma exchange were started. Gradually, there was some neurologic recovery. Aquaporin-4 antibodies were negative and infectious and other autoimmune causes were excluded. Although rare, pediatric onset neuromyelitis optica spectrum disorders occasionally have an exuberant presentation with severe sequelae. The clinical and imagiological features should prompt an early diagnosis and an aggressive immunosuppressive therapeutic.

Keywords: Child; Neuromyelitis Optica/diagnostic imaging; Neuromyelitis Optica/immunology; Neuromyelitis Optica/therapy

Introduction

Neuromyelitis optica spectrum disorders are a group of inflammatory disorders of the central nervous system.[1,2] The causal mechanism is believed to be an autoimmune cascade mediated by the humoral immune system primarily targeting the astrocytes, leading to demyelination and axonal injury, directed mainly at the optic nerves and spinal cord.[1,2] Specific antibodies – aquaporin-4 (AQP4) antibodies – are usually identified.[3] The hallmark features of neuromyelitis optica spectrum disorders are acute attacks of bilateral or rapidly sequential optic neuritis and/or transverse myelitis with a typical relapsing course.[2]

There are no controlled trials evaluating the treatment in pediatric patients. Immune suppression is the cornerstone. Intravenous glucocorticoids and/or therapeutic plasma exchange in acute attacks and long-term prevention with monoclonal antibodies and glucocorticoids.[2]

Case Report

A previously healthy 11 year-old boy, presented to the emergency room on the fourth day of fever (about 38ºC every eight hours), headache, and vomiting. Physical examination showed only a stiff neck, without other neurological changes. Cerebrospinal fluid analysis showed mononuclear pleocytosis (130 cells/µL), hyperproteinorrachia (170 mg/dL), and normal glucose. Viral meningitis was assumed, and he was admitted with support therapy.

On the second day of admission, lower limb pain was noted, with urinary retention and constipation. A neurological examination showed horizontal nystagmiform eye movements (visual acuity not tested), diminished muscular strength in both legs and arms (3/5 in proximal groups, 2/5 in distal groups), and hypoesthesia at the L4-L5 level. Osteotendinous reflexes were normal. Brain and spinal cord magnetic resonance imaging (MRI) showed small ischemic lesions in the deep transition territory in the brain and extensive myelitis from C2-C3 to the *conus medullaris*, predominantly affecting the gray matter.

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An extensive screening for autoimmune and infectious diseases was ordered (Table 1), and broad-spectrum antibiotics (ceftriaxone, ciprofloxacin), acyclovir, and immunoglobulin (2 g/kg) were started.

Neurological symptoms continued to progress rapidly, with an ascending course resulting in complete quadriparesis, autonomic dysreflexia, and bulbar symptoms (dysphagia) on day four. Mechanical ventilation was started. Ophthalmological observation on day five showed bilateral papillitis. Intravenous glucocorticoids were started (1 g methylprednisolone over five days) with no clinical response. Symptoms progressed to cranial nerves palsy (loss of pupillary reflex, facial mimic, and gag reflex as well as vertigo) on day seven.

A second MRI (day eight) showed an increase in supratentorial lesions and gadolinium-enhancing lesions of the optic nerve and chiasm. Due to the disease progression, therapeutic plasma exchange was started with seven sessions of one plasma volume on alternate days, without complications (Spectra Optia® apheresis system).

After the first therapeutic plasma exchange session, there was a slight improvement, with spontaneous eye opening. The patient maintained progressive improvement with the recovery of sensitivity and facial mimicry during the following sessions.

Despite clinical improvement, a third MRI (day 22) showed disease progression with the increased extension of the spinal cord lesions, *de novo* lesions in diencephalic and sublenticular regions as well as greater involvement of the optic nerves and chiasm (Fig. 1). Therefore, intravenous glucocorticoids were repeated, and a second cycle of therapeutic plasma exchange was performed.

An intensive intervention from the physical therapists regarding respiratory autonomy and physical recovery was implemented. After respiratory rehabilitation with intensive cough assist, he was extubated on day 32.

Table 1. Etiologic screening for infections and autoimmune diseases

Molecular biology assays
• Herpesvirus panel on cerebrospinal fluid (EBV, CMV, HSV 1, HSV 2, VZV, and HVH6)
• Enterovirus on cerebrospinal fluid, feces, and nasopharyngeal specimen
• Influenza A and B virus on nasopharyngeal specimen
• Respiratory virus panel on nasopharyngeal specimen (RSV A and B, influenza A, B, C, parainfluenza 1, 2, 3, 4, coronavirus type 229, adenovirus, rhinovirus, bocavirus, echovirus, enterovirus B, metapneumovirus A and B)
• Adenovirus on feces
• *Mycoplasma pneumoniae* on respiratory secretions
• Enterovirus D68 on respiratory secretions
Serology
• EBV: EBNA positive IgG, VCA equivocal IgM and positive IgG
• *Mycoplasma* IgM positive/IgG negative
• CMV and VVZ IgM negative/IgG positive
• *Borrelia* IgM/IgG negative
• Ac. anti-HIV 1 and 2 negative
• *Herpes simplex* I and II IgM/IgG negative;
• Hepatitis C virus negative;
• *Listeria* IgM/IgG negative;
• *Bartonella* IgM/IgG negative;
• *Leptospira* (IgM/IgG and urine) negative
Other infectious assays
• IGRA (TB-spot.TB test) - negative
Autoimmunity
• Serum: ANA, anti-Ro/anti-La, anti-DNAds, anti-SM/RNP/Scl70, anti-ANCA
• Circulating immunoglobulins - normal
• Anti NMO, serum and cerebrospinal fluid - cell based technique and immunofluorescence (Oxford and Heidelberg laboratories) - negative
• Anti-neuronal antibodies (Hu, Yo, Ri, CV2, PNMA2, recov, SOX1, titin), antiganglioside IgM/IgG, anti-nMDAR and anti-MOG - cerebrospinal fluid and serum - negative

Ac. - antibody; ANCA - antineutrophil cytoplasmic antibodies; ANA - antinuclear antibodies; CMV - cytomegalovirus; DNAds - double-stranded DNA; EBNA – Epstein Barr virus nuclear antigen; EBV - Epstein Barr virus; HIV - human immunodeficiency virus; HSV - *herpes simplex* virus; VZV – *varicella zoster* virus; HVH6 - human herpesvirus 6; Ig - immunoglobulin; IGRA - interferon gamma release assay; MOG - myelin oligodendrocyte glycoprotein; nMDAR - N-methyl-D-aspartate; NMO - neuromyelitis optica; PNMA2 - paraneoplastic antigen Ma2; Ri - ; Ro - ; RSV - respiratory syncytial virus; Scl70 - scleroderma 70; SOX1 - Sry-like high-mobility group box protein 1; TB - tuberculosis; VCA - Viral capsid antigen.

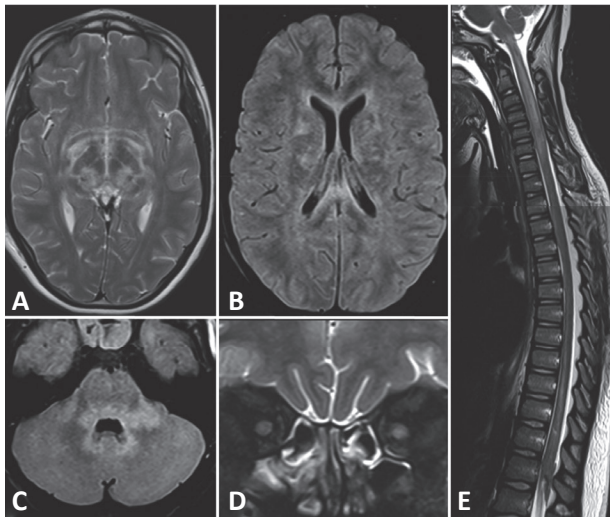

Figure 1. Brain, orbits, and spinal cord magnetic resonance imaging. (a) Axial T2. Diencephalic lesions. (b) Axial fluid-attenuated inversion recovery. Bihemispheric white matter and corpus callosum lesions. (c) Axial fluid-attenuated inversion recovery. Lesions in middle cerebellar peduncles and around the fourth ventricle. (d) Coronal T2 fat suppression. Bilateral optic nerve hypersignal. (e) Sagittal T2. Longitudinally extensive myelitis.

At the end of the second therapeutic plasma exchange cycle, clinical improvement was consistent, and the MRI showed no active lesions, but there were areas of focal reduction of spinal cord thickness, particularly in C6-C7 and in the medullary cone, reflecting early signs of spinal cord necrosis and atrophy (Fig. 2). Maintenance therapy with oral prednisolone (60 mg/day) was started. Serum and cerebrospinal fluid anti-AQP4 (immunofluorescence and cell assay) and other autoantibodies were negative on two international reference laboratories (Oxford and Heidelberg), and neuromyelitis optica spectrum disorder diagnosis was assumed based on the clinical and neuroimaging criteria. Rituximab was started after six months, and corticoids were weaned due to severe side effects (myopathy and weight gain). No relapses have been documented after two years of follow-up. Clinically, he maintained tetraplegia ASIA A: motor strength grade 4/5 in upper limbs, grade 0/5 in lower limbs, anesthesia and analgesia from T2, neurogenic bladder, and no visual defects.

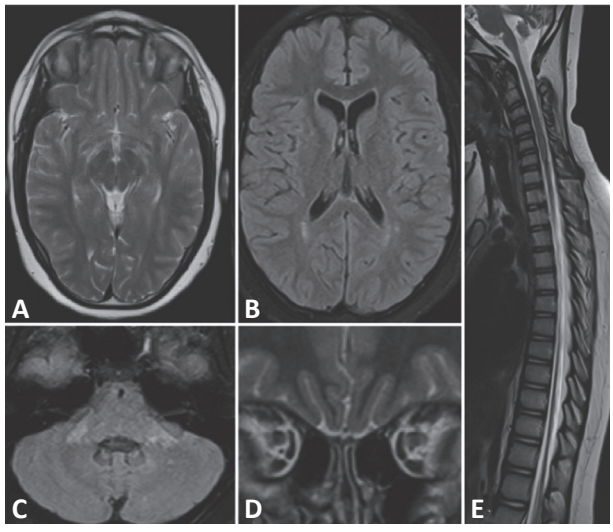

Figure 2. Brain, orbits, and spinal cord magnetic resonance imaging showing the recovery of the lesions. (a) Axial T2. Diencephalic lesions. (b) Axial fluid-attenuated inversion recovery. Bihemispheric white matter and corpus callosum. (c) Axial fluid-attenuated inversion recovery. Middle cerebellar peduncles and around the fourth ventricle. (d) Coronal T2. Bilateral optic nerve without hypersignal. (e) Sagittal T2. Reduction of epidural lipomatosis, although still evidencing the dorsal segment. Marked atrophy of the spinal cord, mainly from C6 to the medullary cone where it is filiform.

Discussion

Neuromyelitis optica spectrum disorders are a group of rare diseases and their specific cause is not totally understood. The common association with other autoimmune disorders and the presence of positive autoimmune markers supports the theory of an autoimmune process mediated by the humoral immune system.[2,4,5] However, the most important fact supporting this theory is the discovery of specific antibodies. Aquaporin-4, the target of neuromyelitis optica immunoglobulin (Ig) G (NMO-IgG), is a water channel protein highly concentrated in spinal cord gray matter, periaqueductal and periventricular regions, and the astrocytic foot process at the blood-brain barrier.[2,6]
Studies in adults show 73% of NMO-IgG seropositivity.[7] In the pediatric population, the results are variable ranging from 30% to 80%.[8-10] Due to the heterogeneity of the assay methods in different centers and the lack of immediate seroconversion, serum tests must be repeated for up to 3-4 years.[5,6,8] Cell-based serum assays are the most specific and sensitive, and although not available in Portugal, they were performed in two reference laboratories in our patient and both were negative.[6,11] The seropositivity rate is lower both in children and adults with monophasic disease, at only 12.5%.[7,12] At this time, it is too early to assume a monophasic course for our patient, but we may consider it because simultaneous optic neuritis and myelitis occur more often in the monophasic course, it is more frequent in children, and monophasic patients experience more severe attacks than our patient.[3,4,6,7,11]
Pediatric onset of neuromyelitis optica spectrum disorders represents only 4% of cases.[8] Diagnosis is often late, but early diagnosis and differentiation from other childhood demyelinating disorders is critical for instituting the appropriate therapy.[8] Multiple sclerosis is the main differential diagnosis.[10]

Neuromyelitis optica spectrum disorders were compared with other childhood demyelinating disorders, and 54% of the patients with neuromyelitis optica spectrum disorders were younger than 11 years, exactly the age of our patient.[8] Other studies also report 10-14 years as being the average age of onset.[4,10] The incidence in women is reported to be up to 10 times higher than in men.[2,9,10] However, female preponderance seems to increase with age, potentially due to puberty.[8] In monophasic neuromyelitis optica spectrum disorders, men and women are equally affected.[2]

The pediatric criteria for diagnosis are similar to those in adults and include seronegative phenotypes.[3,6,9,11,13] In addition to long extensive transverse myelitis and optic neuritis, pediatric-onset is especially characterized by frequent brain involvement at presentation, with encephalopathy or seizures.[1,12] Children often have cerebral lesions (68%),[14] usually involving the diencephalon, brainstem, supra and infratentorial white matter, and cerebellum, which is consistent with the frequent presence of vomiting, altered consciousness, ataxia, and seizures.[4,10,11,14,15] Some studies show optic neuritis (60%)[10] as the most common manifestation in the first attack. In our case, vomiting and brainstem symptoms were present at diagnosis and brain MRI lesions were evident a few days after admission. However, in our patient, spinal involvement was the most prominent factor. Therefore, in spite of seronegativity, the diagnosis was established with the presence of both absolute criteria - optic neuritis and long extensive transverse myelitis, and MRI criteria - spinal cord MRI showing long extensive transverse myelitis and brain MRI not meeting the criteria for multiple sclerosis and lesions in the brainstem and supratentorial area and optic nerve, typical from neuromyelitis optica spectrum disorders.[4,11,14]

Treatment in children is based on adult experience and the acute attack must be treated aggressively and early.[1,15] High dose intravenous methylprednisolone is the first option. However, in non-responsive or severe cases, therapeutic plasma exchange must be considered as first-line therapy.[1,3,4,15] In relapses, the therapy that proved to be the most effective in the first attack must be started promptly.[1,15] There is no consensus about immunosuppressive treatment as prevention therapy. However, it seems to be useful in frequent relapses or after a severe first attack without full recovery.[3,4,15] In our case, we started corticosteroids and, in the absence of clinical improvement, went on to therapeutic plasma exchange. Due to the severity of the attack, we decided to keep the immunosuppression with rituximab due to prednisolone's adverse effects.

Prognosis is poor and disability usually results from the accumulated effects of acute attacks. Predictors of a bad prognosis are the number of relapses in the first two years, the severity of the first attack, older age at onset, and association with other immune diseases.[2,8,15] In our case, the severity of the first attack is the only bad prognosis factor.

In conclusion, neuromyelitis optica spectrum disorders is a rare disease and pediatric onset is even rarer. However, since it can be very disabling and debilitating, it is essential to raise awareness to its presenting features. Initial seronegative results for aquaporin-4 antibodies should not discourage a neuromyelitis optica spectrum disorders diagnosis. Nevertheless, the clinical and imagiological picture should prompt an early diagnosis to allow for administering an early immunosuppressive therapeutic, which is the key to improving the outcome.[1,16]

WHAT THIS CASE REPORT ADDS

- Neuromyelitis optica spectrum disorder is a rare disease and can be very disabling.
- It is essential to raise awareness to its presenting features, and the clinical and imagiological picture should prompt diagnosis.
- Initial seronegative results for aquaporin-4 antibodies should not discourage a neuromyelitis optica spectrum disorder diagnosis.
- Treatment should be based on aggressive immunosuppression.
- Rehabilitation improves the burden and long-term prognosis of the disease.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

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References

1. Crout TM, Parks LP, Majithia V. Neuromyelitis optica (Devic's syndrome): An appraisal. Curr Rheumatol Rep 2016;18:54. doi: 10.1007/s11926-016-0599-3.
2. Glisson CC. Neuromyelitis optica spectrum disorders [accessed 30 June 2020] Available at: https://www.uptodate.pt
3. Trebst C, Jarius S, Berthele A, Paul F, Schippling S, Wildemann B, et al. Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the neuromyelitis optica study group (NEMOS). J Neurol 2014;261:1-16. doi: 10.1007/s00415-013-7169-7.
4. Derle E, Güneş HN, Konuşkan B, Tuncer-Kurne A. Neuromyelitis optica in children: A review of the literature. Turk J Pediatr 2014;56:573-80.
5. Domingos J, Isidoro L, Figueiredo R, Brum M, Capela C, Barros P, et al. Neuromyelitis optica in Portugal (NEMIPORT): A multicentre study. Clin Neurol Neurosurg 2015;134:79-84. doi: 10.1016/j.clineuro.2015.04.001.
6. Franciotta D, Gastaldi M, Sala A, Andreetta F, Rinaldi E, Ruggieri M, et al. Diagnostics of the neuromyelitis optica spectrum disorders (NMOSD). Neurol Sci 2017;38:231-6. doi: 10.1007/s10072-017-3027-1.
7. Banwell B, Tenembaum S, Lennon VA, Ursell E, Kennedy J, Bar-Or A, et al. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. Neurology 2008;70:344-52. doi: 10.1212/01.wnl.0000284600.80782.d5.
8. Chitnis T, Ness J, Krupp L, Waubant E, Hunt T, Olsen CS, et al. Clinical features of neuromyelitis optica in children: US network of pediatric MS centers report. Neurology 2016;86:245-52. doi: 10.1212/WNL.0000000000002283.
9. Fragoso YD, Ferreira ML, Oliveira EM, Domingues RB, Ribeiro TA, Brooks JB, et al. Neuromyelitis optica with onset in childhood and adolescence. Pediatr Neurol 2014;50:66-8. doi: 10.1016/j.pediatrneurol.2013.07.003.
10. Lee LE, McMullen K, Carruthers R, Traboulsee A, Characterizing pediatric-onset neuromyelitis optica spectrum disorder in British Columbia. BCMJ 2016;59:25-9.
11. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89. doi: 10.1212/WNL.0000000000001729.
12. Collongues N, Marignier R, Zéphir H, Papeix C, Fontaine B, Blanc F, et al. Long-term follow-up of neuromyelitis optica with a pediatric onset. Neurology 2010;75:1084-8. doi: 10.1212/WNL.0b013e3181f39a66.
13. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-15. doi: 10.1016/S1474-4422(07)70216-8.
14. Kim HJ, Paul F, Lana-Peixoto MA, Tenembaum S, Asgari N, Palace J, et al. MRI characteristics of neuromyelitis optica spectrum disorder: An international update. Neurology 2015;84:1165-73. doi: 10.1212/WNL.0000000000001367.
15. Kleiter I, Gold R. Present and future therapies in neuromyelitis optica spectrum disorders. Neurotherapeutics 2016;13:70-83. doi: 10.1007/s13311-015-0400-8.
16. Bonnan M, Valentino R, Debeugny S, Merle H, Fergé JL, Mehdaoui H, et al. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. J Neurol Neurosurg Psychiatry 2018;89:346-51. doi: 10.1136/jnnp-2017-316286.

Mielite Transversal Longitudinal Extensa: Um Desafio Diagnóstico e Terapêutico

Resumo:
Os transtornos do espetro de neuromielite óptica são distúrbios inflamatórios do sistema nervoso central, caracterizados por desmielinização imunomediada e lesões dos axónios, tendo como alvo predominante os nervos ópticos e a medula espinhal. Relatamos o caso clínico de um menino de 11 anos, internado por suspeita de meningite viral. Passadas 24 horas da admissão, desenvolveu disfunção vesical e perda sensorial ascendente progressiva. A ressonância magnética do cérebro e medula espinhal mostraram uma mielite extensa. Foi iniciado tratamento com antibióticos de largo espetro e imunoglobulinas. Os sintomas neurológicos continuaram a evoluir e uma fundoscopia revelou uma papilite óptica bilateral. Uma ressonância magnética realizada ao oitavo dia evidenciou progressão das lesões e comprometimento do nervo óptico, sugerindo transtornos do espetro de neuromielite óptica. Foram iniciados corticoides em doses elevadas, seguidos de plasmaferese. Gradualmente, verificou-se alguma recuperação neurológica. Os anticorpos aquaporina-4 foram negativos e as causas infeciosas e outras causas autoimunes foram excluídas. Embora raros, os transtornos do espetro de neuromielite óptica de início pediátrico apresentam ocasionalmente uma apresentação exuberante e sequelas graves. O quadro clínico e imagiológico permite o diagnóstico precoce e a instituição de terapêutica imunossupressora agressiva.

Palavras-Chave: Criança; Neuromielite Óptica/diagnóstico por imagem; Neuromielite Óptica/imunologia; Neuromielite Óptica/tratamento