CASE REPORT

Acute gastroenteritis and unilateral vision loss leading to a diagnosis of aquaporin-4-IgG seropositive neuromyelitis optica spectrum of disorders in a child: A case of atypical optic neuritis in the era of biomarkers

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Neuromyelitis optica spectrum of disorders is a rare cause of optic neuritis in children. It is a critical diagnosis requiring urgent management, with delays carrying both life- and sight-threatening complications. Most of the published literature on this entity is in adult patients, with only a few case reports to guide management in the paediatric population. The purpose of this article is to shareour experience in the management of this condition in a child, and thus hopefully add to the limited body of knowledge currently available.

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Neuromyelitis optica spectrum of disorders (NMOSD) is rare in the paediatric population.[1] It is an important differential to consider as it typically runs a more severely debilitating course than multiple sclerosis and other demyelinating disease, and is associated with a 5-year mortality rate of 30% worldwide.[2] Paediatric optic neuritis accounts for 25% of acute demyelinating syndromes in this age group.[3,4] Post-infectious (usually viral) or post-immunisation aetiologies usually predominate.[5] Less commonly, it may be the first manifestation of multiple sclerosis (MS) or other diffuse demyelinating disorders such as acute demyelinating encephalomyelitis (ADEM), NMOSD and myelin oligodendrocyte glycoprotein-associated disease (MOGAD).[5,6]

First described by Devic and Gault over a century ago, neuromyelitis optica affects the optic nerve and spinal cord preferentially.[6] Approximately only 4% of NMOSD is of paediatric onset.[2] In contrast to adult optic neuritis, the clinical picture is more often an anterior rather than a retrobulbar optic neuritis, associated with a marked decrease in vision.[6] The challenge is that young children may not notice or report vision loss until changes in their behaviour alert a parent or caregiver. A flu-like prodrome is often elicited on careful history preceding the onset of vision loss.[7]

The pathophysiological mechanisms of inflammation in paediatric optic neuritis are thought to be due to cross-reacting viral and host epitopes. NMOSD is essentially an astrocytopathy caused by autoantibodies (IgG) attacking aquaporin-4 (AQP4) water channels found in the foot processes of astrocytes.[7,8] Initially thought to be part of the spectrum of disease attributed to MS, it is now understood to be a clearly distinct clinical and immunological entity causing visual loss, disability and even death in severe cases.[9] Historically thought to be limited to optic nerve and spinal cord lesions, it is now appreciated to affect areas populated with AQP4 transmembrane channels, namely peri-ependymal, medulla oblongata and hippocampal.[8-10]

Case report

OL, a 10-year-old girl, presented to Red Cross War Memorial Children's Hospital eye clinic with a history of sudden painful loss of vision in her left eye 3 months before, following an episode of severe gastric flu for which she had been admitted to her base hospital for intravenous antibiotics and fluids, with a diagnosis of 'tonsillitis and gastroenteritis' for a few days. Of note, she also described left-sided facial and body weakness with difficulty walking, which was still present on discharge from hospital. She had not been worked up nor referred for her visual or neurological complaints at that point. It took approximately a month for her gait to return to baseline on further enquiry. Her present complaint was weakening of vision in her left eye and persistent 'dragging' of her left foot, with recurrent left-sided body weakness. There were no current gastrointestinal symptoms nor pain. She was an otherwise healthy child with no comorbidities. Interestingly, there was a family history of myasthenia gravis (MG), with her father having been diagnosed a few years earlier.

Examination revealed a Snellen vision of 6/6 right eye and counting fingers (no improvement on pinhole testing) left eye, with a brisk relative afferent pupillary defect. There was marked red desaturation on colour vision testing of her left eye. Ocular motility testing was noted to be normal. Further examination revealed an otherwise normal right eye examination. Her left eye had a normal anterior segment, but blurring of her optic disc margins with temporal pallor was noted on fundoscopy. There were no vitreous cells and no other fundal abnormalities. There was marked red desaturation and diminished light brightness appreciation of her left eye. On systemic examination she was haemodynamically stable with mild diminution of power of her left lower limb and down-going plantar reflexes in both feet. There was decreased sensation over her abdomen, more so on the left. The rest of her neurological examination was non-contributory.

A provisional diagnosis of an atypical optic neuritis secondary to demyelination, infection or inflammation was made. An infective and inflammatory panel of blood tests was done, including AQP4, MOGAD and acetylcholine receptor antibodies. A magnetic resonance imaging (MRI) scan was ordered, and referral to neurology was done on an emergency basis. She was subsequently admitted under neurology, and intravenous (IV) methylprednisolone pulsing over 5 days commenced.

MRI brain and orbits (Fig. 1) revealed expansion and abnormal enhancement of her left optic nerve extending up to the level of the optic chiasm, with associated inflammatory fat stranding in the orbit. Spinal MRI (Fig. 2) revealed longitudinally extensive transverse myelitis from C2 to C6. Cerebrospinal fluid analysis was negative for oligoclonal bands and showed no cells on microscopy. At this junction, the diagnosis of NMOSD seemed most likely. Infective and autoimmune panels were all negative.

With minimal response to steroid pulsing, the decision was made to escalate to plasma exchange (PLEX) for five cycles, followed by initiation of rituximab infusion therapy. On initiation of rituximab infusion therapy, she experienced a generalised papular urticarial reaction. A successful densensitisation protocol was implemented, with no further complications. Serum AQP4-IgG antibody was positive with a high titre of 100, confirming the diagnosis in her second week of admission. After 6 weeks she was discharged from the ward with vision in her left eye 6/36, normal gait and no residual neurological fallout save for a small area of hypoaesthesia involving her lower left trunk.

Discussion

It is critical to distinguish NMOSD from MS and other causes of demyelinating childhood disorders so that correct treatment can be instituted early. The significant delays often encountered in instituting appropriate therapy for NMOSD compared with paediatric MS leadsto poorer outcomes.[9-11] A diagnosis of NMOSD generally confers a much worse prognosis than MS, ADEM or MOGAD.[9] About 50% of seronegative NMOSD patients may test positive for myelin oligodendrocyte (MOG) antibodies.[9,11] Further confounding the picture is that patients with ADEM can frequently test positive for MOG antibodies.[12,13] MOG antibody positivity, however, confers a milder clinical phenotype with generally good visual recovery.[7,8] Importantly, it is extremely unlikely that a patient will test positive for both AQP4 and MOG antibodies simultaneously.[13,14]

Management of paediatric NMOSD is generally guided by experience in adults. An international Delphi consensus on AQP4-IgG-positive NMOSD in May 2023 provided guidance in terms of management being stratified into two prongs, the first being treatment of the acute attack and the second being long-term immunosuppressant maintenance therapy for relapses.[15] NMOSD is typically not a monophasic condition, and relapses run a generally more severe course with greater debility.[14,15] Relapses may span a few days from the initial attack to months or even years.[14,15]

For acute attacks, the accepted standard treatment is high dose IV corticosteroids,[12,16] typically methylprednisolone, as was used in our patient over 3 - 5 days. There is a low threshold to escalate to PLEX in patients not responding to IV corticosteroids,[12,16] as was also the case in our patient. Prior to 2019 a variety of immunosuppressive drugs used off-label were used as typical maintenance therapy, such as mycophenolate mofetil, rituximab and azathioprine.[8,11,15] Many countries around the world have started using the three new US Food and Drug Administation-approved biological therapies with success,[15] although they are not readily available in the state sector in South Africa (SA) yet due to exorbitant costs. Rituximab was successfully used in the management of our patient following a desensitisation protocol after a suspected anaphylactoid reaction. No complications were reported while on maintenance rituximab infusion therapy.

Lastly, there have also been a few case reports in the literature describing NMOSD occurring in the setting of MG. This does make sense clinically considering both are autoimmune channelopathies and are also associated with other autoimmune diseases including systemic lupus erythematosus, Sjögren syndrome, Grave's disease and rheumatoid arthritis. In most cases, MG precedes the onset of

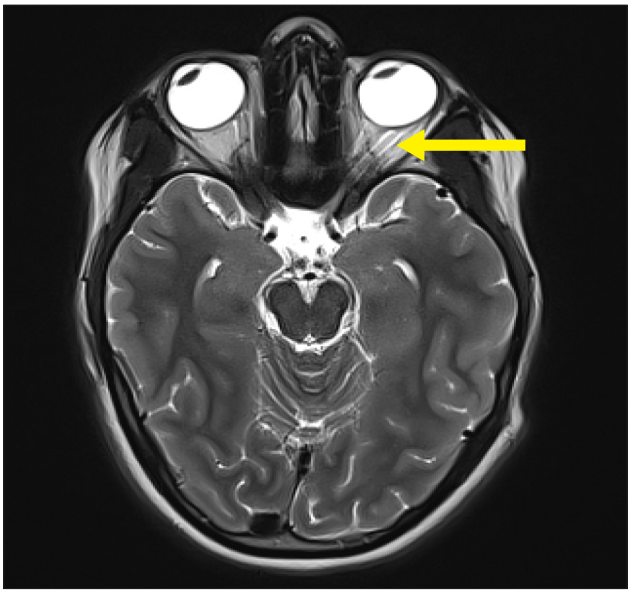

Fig. 1. Sagittal magnetic resonance imaging brain and orbits scan showing enhancement of the left optic nerve up to the optic chiasm.

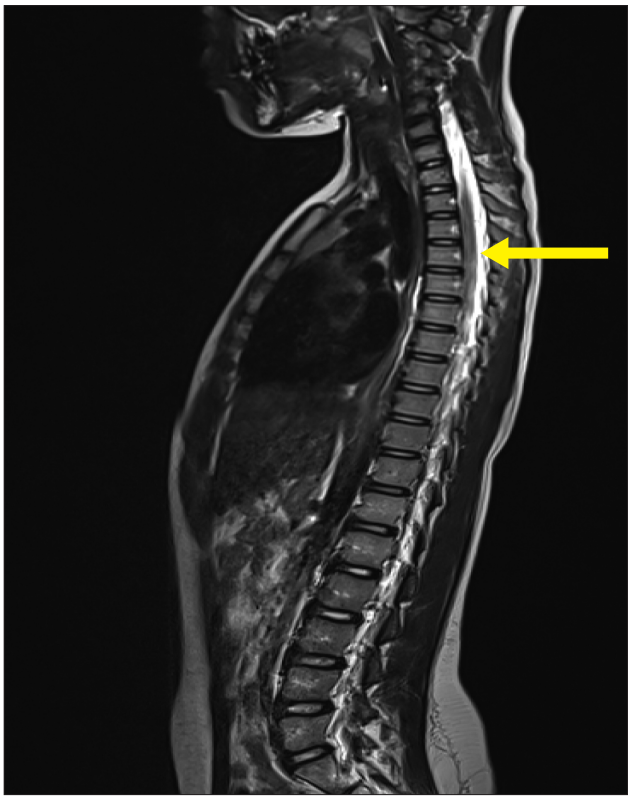

Fig. 2. Spinal magnetic resonance imaging scan showing expansion of the spinal cord from C2 to C6 with T2 hyperintensity suggestive of oedema.

NMOSD and runs a generally benign course.[17] Acetylcholine receptor antibodies (AChR-Abs) or AQP4-Abs may be present years before the onset of either disease.[17] While our patient tested negative for AChR-Abs, it was interesting to note that her father was known to have the diagnosis of MG. Our patient was diagnosed with autoimmune hypothyroidism during her protracted inpatient stay. It is important to be aware of the association between these two rare autoimmune diseases as well as other autoimmune diseases affecting the eye (thyroid-associated especially), as prompt and correct diagnosis has implications in terms of management and prognosis.[16-18]

Teaching points

- NMOSD is an important differential for atypical optic neuritis as it can result in severe disability or death if missed.
- AQP4 antibody is an important biomarker for diagnosis of NMOSD.
- Newer biological therapies are available for treatment of NMOSD.
- Early referral to neuro-ophthalmic services is critical to institute sight and life-saving therapies.

Conclusion

The diagnosis and management of atypical optic neuritis in the current era of biomarkers have evolved alongside our understanding of the basic pathophysiology of this neuro-ophthalmic entity. NMOSD is a life-threatening and often severely debilitating diagnosis in adult patients. It is critical to keep this important differential in mind when assessing a child with features of atypical optic neuritis, as prompt referral and treatment improve clinical outcomes.

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