CASO CLÍNICO/CASE REPORT

Simultaneous Diagnosis of Early-Onset Neuromyelitis Optica Spectrum Disorder and Autoimmune Thyroid Disease

Diagnóstico Simultâneo de Doença do Espectro da Neuromielite Óptica de Início Precoce e Doença Tiroideia Autoimune

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Abstract

Pediatric optic neuritis may arise in isolation or as part of the manifestations of an inflammatory and demyelinating disorder of the central nervous system. Clinical presentation and prognosis are widely variable, depending on the etiology. We describe a 13-year-old patient, which presented with unilateral optic neuritis, which lead to a simultaneous diagnosis of early-onset neuromyelitis optica spectrum disorder with positive antibodies against the aquaporin 4 channel (AQP4-IgG) and subclinical hypothyroidism with positive serum thyroid antibodies. Neuromyelitis optica spectrum disorders are a rare group of demyelinating autoimmune diseases that predominantly affect the optic nerve and spinal cord. Associated autoimmunity is common at onset, with frequent positive antibody titers both organ-specific and non-organ-specific. It is crucial to recognize the particularities in pediatric neuromyelitis optica spectrum disorder and the multiple entities to consider in the differential diagnosis, in order to establish the appropriate management.

Resumo

A nevrite óptica em idade pediátrica pode surgir de forma isolada ou associada a doença desmielinizante do sistema nervoso central. A apresentação clínica e o prognóstico são muito variáveis, dependendo da causa subjacente. Os autores descrevem o caso de uma adolescente de 13 anos que se apresentou com quadro clínico compatível com nevrite óptica unilateral, que conduziu ao diagnóstico simultâneo de doença do espectro da neuromielite óptica com positividade para anticorpos dirigidos aos canais de aquaporina 4 (AQP4-IgG) e hipotiroidismo subclínico, também com autoanticorpos positivos. O espectro da neuromielite óptica é definido por um grupo heterogéneo de doenças inflamatórias do sistema nervoso central que predominantemente afetam o nervo óptico e a medula espinhal, de expressão rara na nossa população. A presença de autoimunidade concomitante é comum, com autoanticorpos positivos, tanto órgão-específicos como não órgão-específicos. É fundamental reconhecer as particularidades desta patologia em idade pediátrica, bem como o seu diagnóstico diferencial, permitindo a orientação terapêutica mais adequada.

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Introduction

Pediatric optic neuritis may arise in isolation or as part of the manifestations of an inflammatory and demyelinating disorder of the central nervous system (CNS).[1,2] Neuromyelitis optica spectrum disorders (NMOSD) are a rare group of ever-expanding autoimmune disorders that predominantly affect the optic nerve and spinal cord, while also involving other areas of the CNS.[2,3] NMOSD are also associated with other autoimmune diseases, with frequent positive antibody titers, both organ-specific and non-organ-specific.[3] The association of autoimmune thyroiditis and NMOSD is an uncommon yet well recognized event in adults. In children, it has rarely been described. We report a case of early-onset neuromyelitis optica spectrum disorder, which concurrently presented with subclinical hypothyroidism, with positive serum thyroid antibodies. Our case highlights the importance of early diagnosis of both disorders, since underdiagnosing coexisting autoimmune disease in NMOSD may impact treatment and outcome.

Case Report

A previously healthy and fully vaccinated 13-year-old girl presented to our emergency department (ED) after two months of blurred central vision and retro-orbital right eye pain associated with ocular movement. Patient's review of systems was otherwise negative. She denied fever, photophobia, headache, rashes, vomiting or loss of consciousness. There was no recent history of trauma, acute illness, travel or other suspicious exposure. She had no relevant past medical history nor was she previously prescribed medication. Her growth curves were harmonious, with proper developmental milestones and no signs of learning difficulties. Family history was relevant for vitiligo and rosacea in her mother, but not for eye or neurological disorders. On admission, she had normal mental status and vital signs and physical examination was unremarkable, except for low visual acuity, without other neurological deficits. Ocular examination revealed visual acuity in the right eye of < 0.1 with an ipsilateral relative afferent pupillary defect, central scotoma on visual field evaluation and signs of optic atrophy on fundoscopy. Baseline blood work and brain and orbit computed tomography scans were normal. A diagnosis of unilateral optic neuritis was made and she was admitted for further investigation and management. The on-call neurologist confirmed neurological examination results and further study with magnetic resonance imaging (MRI) showed signs of edema and hyperintensity involving the right optic nerve and the optic chiasm, compatible with the clinical diagnosis of optic neuritis (**Fig. 1**). She was transferred to a level III

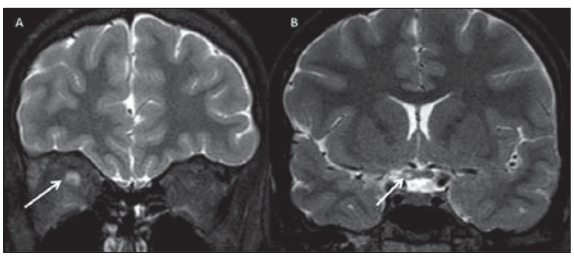

Figure 1. Brain MRI (coronal T2-weighted images) showing (A) a hyperintense lesion involving the right optic nerve (arrow); (B) the lesion extends to the optic chiasm (arrow).

hospital for evaluation by Pediatric Neurology. Extensive workup included serum and urine toxicology, viral serologies, cerebrospinal fluid (CSF) analysis, thyroid function tests and autoimmune screening studies. Toxicology study was negative. Infectious etiologies as Herpesviridae, HIV, tuberculosis and toxoplasmosis were excluded. CSF testing was found to be normal, with no oligoclonal IgG bands. Thyroid screening revealed elevated thyroid-stimulating hormone (TSH), normal free thyroxine (T4) and positive thyroid autoantibodies, namely anti-thyroperoxidase (TPOAb) and anti-thyroglobulin (TgAb) antibodies. Serum sample was positive for aquaporin 4-directed antibodies (AQP4-IgG) and antinuclear antibodies (ANA) (1:320 titer) and negative for antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG). A diagnosis of neuromyelitis optica spectrum disorder was made. She started high-dose intravenous corticosteroids with improvement on right visual field and was discharged after a week. She was also referred to a Pediatric Endocrinologist to continue surveillance of her thyroiditis with subclinical hypothyroidism, with normal thyroid ultrasound.

During early outpatient follow-up, she showed signs of stabilization of disease with azathioprine. Approximately one year later, she was again admitted to the ED with a 3-day course of cervical pain, right upper limb paresthesia and right eye continuous nystagmus. She underwent a brain and spinal cord MRI, which confirmed the presence of a longitudinally extensive myelitis, reinforcing the active progression of this condition (**Fig. 2**). She was treated with high-dose intravenous methylprednisolone, with clinical improvement and discharged after a week. She maintains regular follow-up by the Pediatric Demyelinating Disorders medical team and a switch from azathioprine to rituximab (an anti-CD20 monoclonal antibody) was performed.

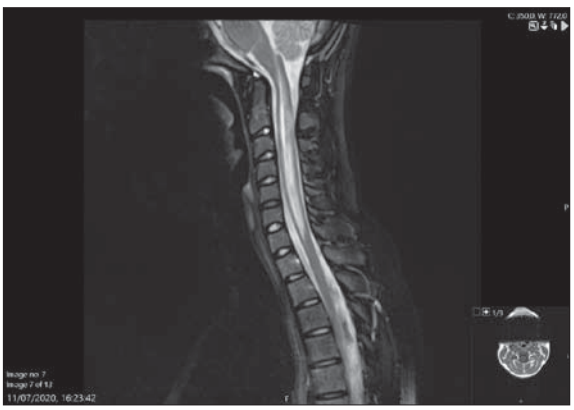

Figure 2. Brain MRI (coronal T2-weighted images) showing a hyperintense medullar lesion that extends from bulbomedular transition to C7 with spinal cord expansion.

Discussion

Pediatric optic neuritis is a rare disorder that clinically manifests through acute visual loss.[1] It may arise as a distinct condition or as part of an inflammatory and demyelinating disorder of the CNS.[1,2] Diagnosing CNS demyelinating diseases in children is challenging, not only because of the extensive differential diagnosis, which includes infectious, neoplastic, metabolic and autoimmune etiologies, but also as there are few specific markers and tests available.[3] In addition, self-limited and chronic conditions may be indistinguishable at initial presentation and prognosis is widely variable, depending on etiology.

NMOSD are an ever-expanding group of rare autoimmune disorders predominantly targeting optic nerves and the spinal cord.[4] Initially considered a subtype of multiple sclerosis, nowadays it is known that NMOSD are distinct entities, with a phenotype which includes more subforms than the classic disease described by Devic.[4] NMOSD predominantly affect female adults in the fourth decade of life, but up to 5% of cases occur in children, with typical age of onset from 10 to 12 years.[3,4] The classic clinical manifestation involves recurrent episodes of optic neuritis and myelitis with incomplete recovery between attacks.[4,5] Particularly suggestive of NMOSD is bilateral optic neuritis, involving the optic chiasm, associated with visual field defect or with severe visual loss.[4] AQP4-IgG seropositivity occurs in approximately 65% of pediatric patients with NMOSD and it may not be present at the initial episode.[5] Other helpful laboratory features are pleocytosis with lymphocyte predominance and absence of oligoclonal bands in CSF testing.[4,5] Brain MRI may also play a significant role in distinguishing typical multiple sclerosis from NMOSD lesions. Our case fulfilled the diagnostic criteria with a core manifestation (optic neuritis), a positive test for AQP4-IgG and exclusion of secondary causes.

An ever-growing list of autoimmune disorders, both organ-specific and non-organ-specific, including myasthenia gravis, systemic lupus erythematosus, Sjogren's syndrome, celiac disease and sarcoidosis, have been associated in up to 20%–30% of patients with NMOSD and may present before or after the development of CNS demyelination.[6] Autoantibodies are also found in patients with NMOSD without coexisting disease, which is probably due to an overall heightened immune response.[6] The excess of autoimmunity in these patients is yet to be fully understood.[7] The particular association of NMOSD with autoimmune thyroiditis has been rarely reported.[7] Additionally, the presence of thyroid autoantibodies in the serum of healthy people is common, including in children. Positive serum thyroid antibodies could alternatively point to Hashimoto's encephalopathy. Encephalopathy associated with autoimmune thyroid disease is a controversial entity, as its pathophysiology is not yet well defined, usually being a diagnosis of exclusion.[7,8] It is known to be associated with clinical or subclinical autoimmune thyroid disease, most commonly Hashimoto's thyroiditis. Given the clinical presentation and positive neuronal antibodies for another disease, this diagnosis was excluded.[8] Neurological manifestations in autoimmune thyroid disease continue to present a diagnostic dilemma, as patients present with a wide spectrum of presentations, ranging from unspecific symptoms, like cognitive or behavioral disturbances, tremor, myoclonus or ataxia, to more severe conditions, such as seizures, stroke-like episodes and motor dysfunction.[8] The pathogenic role of thyroid autoantibodies is yet to be fully understood.

Although new therapies are emerging, there is still no definitive treatment for NMOSD.[5] Current first-line approach usually includes high-dose systemic corticosteroids during acute attacks to induce remission and improve relapse-associated symptoms, as well as long-term immunosuppression to attempt stabilization of disease course.[5] However, overall prognosis is markedly unfavorable, with most patients (70% to 90% in most cohorts) experiencing a new relapse within the first 2 years after the diagnosis, resulting in incremental disability and/or mortality due to transverse myelitis and respiratory failure.[9,10] Early age at disease onset seems to be a predictor of poor visual outcome, while motor disability is more associated with older age at disease onset.[10] Further studies are needed to compare the eventual difference between pediatric and adult-onset NMOSD prognosis.

Conclusion

NMOSD are a rare and underrecognized group of diseases in children, with an overall homogenous presentation. Early recognition and management can significantly improve prognosis, which is nevertheless poor, with inevitable progression toward cumulative morbidity. Long-term follow-up is required to assess new complaints and disabilities, medication side effects and monitoring relapses. More studies in the pediatric population with NMOSD are required for a better understanding of its pathophysiology and future treatment research. This case serves as a reminder not only of a rare condition one must not miss, with wide clinical heterogeneity, but also illustrates the difficulties in establishing a diagnosis and inferring on the prognosis, particularly at such an early stage of life. ■

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