

Received: 2020.04.17

Accepted: 2020.08.04

Available online: 2020.08.26

Published: 2020.10.07

Internuclear Ophthalmoplegia as the First Manifestation of Pediatric-Onset Multiple Sclerosis and Concurrent Lyme Disease

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1 **Jonathan Chao**
EF 2 **Sandal Saleem**
E 1 **Hassan N. Tausif**
E 2 **Kelly Levasseur**
E 1 **Lori A. Stec**

1 Beaumont Eye Institute Department of Ophthalmology, William Beaumont Hospital, Royal Oak, MI, U.S.A.

2 Department of Pediatric Emergency Medicine, William Beaumont Hospital, Royal Oak, MI, U.S.A.

Corresponding Author: Jonathan Chao, e-mail: jonathan.chao@beaumont.org

Conflict of interest: None declared

Patient: Female, 16-year-old
Final Diagnosis: Multiple sclerosis
Symptoms: Blurry vision
Medication: —
Clinical Procedure: Lumbar puncture • magnetic resonance imaging
Specialty: Ophthalmology

Objective: Rare co-existence of disease or pathology

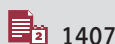
Background: Internuclear ophthalmoplegia (INO) presents as a disruption of horizontal conjugate ocular movement and is an uncommon finding in the pediatric population. Its presence warrants a thorough evaluation to search for demyelinating, mass effect, inflammatory, or infectious etiologies.

Case Report: A 15-year-old African American girl presented to the Emergency Department with acute horizontal binocular diplopia in left gaze. An ophthalmic examination revealed a right INO. She denied any fever, chills, or neck stiffness. Complete blood counts and a metabolic panel were unremarkable. Magnetic resonance imaging (MRI) of the brain and orbits revealed scattered pontine, periventricular, and subcortical white matter signal abnormalities within the left frontal lobe suggestive of active demyelination. MRI of the spinal column also demonstrated multiple areas of increased signal intensity from the C3 to C7–T1 region. Inflammatory and autoimmune studies were negative. However, her serum IgM and IgG studies were positive for *Borrelia burgdorferi* with negative CSF titers. Cerebrospinal fluid (CSF) analysis demonstrated mildly elevated glucose (82 mg/dL) and oligoclonal bands, but was otherwise unremarkable. She was started on intravenous methylprednisolone and ceftriaxone. She was subsequently diagnosed with pediatric-onset multiple sclerosis and started on disease-modifying therapy, with full resolution of diplopia and INO 2 weeks later.

Conclusions: We present a case of INO presenting as the first manifestation of multiple sclerosis in a pediatric patient with a concurrent infectious etiology. A thorough evaluation can lead to earlier identification and treatment of underlying diseases.

MeSH Keywords: Lyme Disease • Multiple Sclerosis • Ocular Motility Disorders

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/925220>



1407



—



2



1



21



Background

Internuclear ophthalmoplegia (INO) presents as a disruption of horizontal conjugate gaze. Lesions involving the medial longitudinal fasciculus result in an adduction deficit with decreased saccadic velocity ipsilateral to the side of the lesion, often with a dissociated abducting nystagmus in the contralateral eye. INO in the adult population is frequently the result of a demyelinating disease such as multiple sclerosis (MS) or an ischemic cerebrovascular accident. Less common causes include trauma, tentorial herniation, intracerebral hemorrhage, vasculitis, and infection [1]. MS is most commonly diagnosed in young adults and presents much less frequently in children before age 16 years. There have been few reports of pediatric INO secondary to a demyelinating disease such as MS, and it remains a rare ophthalmic finding in the pediatric population [2]. Therefore, accurate identification of INO in children and appropriate neurological investigation is crucial for timely diagnosis of such neurologic diseases and initiation of disease-modifying therapy. We present a case of a patient with pediatric-onset MS with concurrent Lyme disease whose presenting sign was INO.

Case Report

An otherwise healthy 15-year-old African American girl presented to the Emergency Department (ED) with 2 weeks of a mild headache that improved with ibuprofen, acetaminophen, and aspirin-paracetamol-caffeine. During this time, she was told by her friends and family that her eyes appeared “unnatural and twitchy” when looking to the left side. Ophthalmology was consulted for her visual disturbances. On examination, her visual acuity was 20/20 in both eyes (OU). Her visual fields were full on confrontation, intraocular pressures were within normal limits, and her pseudoisochromatic plates were full. Her pupils were equal and reactive to light without an afferent pupillary defect (APD). Extraocular motility was significant for incomplete adduction with decreased saccadic velocity in the right eye (OD) with an associated horizontal abducting nystagmus in the left eye (OS), consistent with a right internuclear ophthalmoplegia (INO) (Figure 1, Video 1). Examinations of her anterior and posterior segments were otherwise unremarkable. A magnetic resonance imaging (MRI) of the brain and orbits with contrast gadolinium demonstrated scattered bilateral foci of periventricular and subcortical deep white matter T2/FLAIR signal hyperintensities. Additionally, she had 2 enhancing white matter foci within the left frontal lobe, measuring 5 mm and 6 mm (Figure 2). There were additional foci of abnormal signaling within the pons, genu, and splenium that did not have postcontrast enhancement. Her optic nerves and chiasm did not demonstrate pathologic enhancement. A magnetic resonance angiography (MRA) of the brain



Figure 1. Extraocular movements in right, primary and left gaze. Note the limitation in adduction of the right eye. There is an associated contralateral nystagmus of the left eye with attempted left gaze.



Video 1. Decreased saccadic velocity with right adduction when the patient is asked to re-fixate quickly between 2 stationary targets.

was unremarkable. MRI studies of her cervical, thoracic, and lumbar spine revealed multiple areas of increased signaling from C3 to C7-T1 region with additional white matter T2 hyperintensities in the cervicomedullary junction.

Laboratory test results were negative for inflammatory and autoimmune markers, including C-reactive protein (CRP),

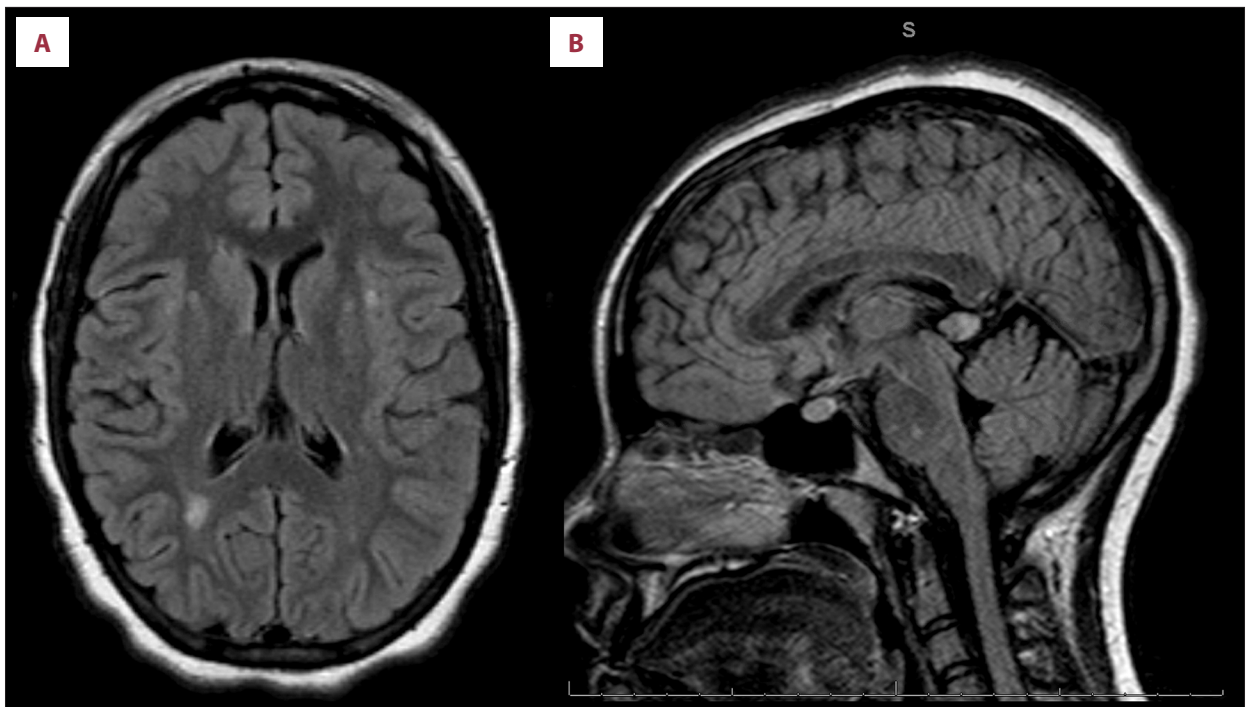


Figure 2. Magnetic resonance imaging of the head using T2/FLAIR sequencing. (A) Scattered bilateral foci of periventricular and subcortical deep white matter. An axial section demonstrating an active demyelinating lesion of the left and posterior right cortical regions. (B) Sagittal image of foci of abnormal signal within in the pons. Of note, there is an incidental benign cystic enlargement of the pineal gland.

anti-Sjogren SSA antibody, anti-Sjogren SSB antibody, anti-nuclear antibody (ANA), anti-double stranded DNA antibody (dsDNA), and angiotensin-converting enzyme (ACE). An anterior-posterior-chest X-ray was negative for hilar adenopathy. Human immunodeficiency virus (HIV) assay and syphilis testing were negative. Her serum bloodwork was positive for IgG and IgM antibodies to *Borrelia burgdorferi* but cerebrospinal fluid (CSF) titers of IgG and IgM and culture were negative. An additional CSF study was significant for oligoclonal bands. Neuromyelitis optica (NMO) evaluation for anti-aquaporin-4 antibody was negative.

She was started on 1 g per day of intravenous methylprednisolone for 3 days in consultation with Neurology for suspicion of juvenile MS due to significant white matter disease on the MRI. She was started on ceftriaxone 2 g for *Borrelia burgdorferi* and subsequently discharged with a 2-week course of doxycycline. Upon follow-up with a pediatric neurologist, her diagnosis was categorized as intermittent relapsing multiple sclerosis based on revised McDonalds criteria, which included CSF-specific oligoclonal bands and lesions separated by time based on radiographic findings within the cortex and spinal cord. The patient was started on disease-modifying therapy (DMT) with interferon beta. Her diplopia and INO had resolved upon her follow-up visit with the neurologist 2 weeks after discharge.

Discussion

Pediatric internuclear ophthalmoplegia (INO) is infrequently described in the literature, but there are case reports related to vascular infarcts secondary to sickle cell disease, mild head injury, intraparenchymal tumors, ischemic stroke with a patent foramen ovale, and encephal meningitis [3–8]. INO is a rare finding in pediatric-onset MS. In a retrospective review of 17 children with a mean age of 13.5 years with definite multiple sclerosis, 12 presented with optic neuritis and 4 had brainstem symptoms (1 with sixth cranial nerve palsy, 2 with INO, and 1 with one and a half syndrome) [2]. Appreciation of INO in the pediatric population may be complicated by a difficult and uncooperative examination [5]. Nonetheless, it is crucial to identify INO, as it may be the first sign of an underlying illness and has discrete and localization value to aid in accurate diagnosis.

MS is most commonly diagnosed in young adults and presents much less frequently in children before the age of 16 years. A longitudinal study by Boiko et al. reported a prevalence of 3.6% in early-onset MS, which was defined as a diagnosis of MS prior to the age of 16 years, over a mean observation follow-up period of 19.76 years, with the majority of patients following a relapsing-remitting course [9]. In their study, the most common presenting symptoms were sensory

disturbances (25.9%) followed by optic neuritis (21.6%). Their study is consistent with other reports regarding the prevalence of early-onset MS, which accounts for 3% to 5% of all MS cases [10]. Ghezzi et al. performed a retrospective review of 3375 patients with clinically definite or probable MS and found 149 (4.4%) presented before the age of 16 years, with a female-to-male ratio of 2: 2 [11]. Brainstem dysfunction was reported to be the most frequent initial presenting symptom (25%), followed by diplopia (20.3%). There was no further delineation of the cause of diplopia. Similarly, in Duquette's report of 125 patients with MS onset before age 16 years, the most common presentations were sensory (26.4%), optic neuritis (14%), diplopia (11%), and pure motor (11%) [10]. Likewise, there was a strong predominance of involvement in females, relapsing-remitting type, and fair prognosis of disease progression at 15 years, which they described as non-wheelchair-bound.

Disease-modifying therapies are widely used in adult patients with MS, with the greatest impact experienced when initiated early in the disease course [12]. Several studies suggest lower risk of MS progression following initiation of immunomodulatory drugs [13–15]. Similar efficacies may apply to pediatric relapsing-remitting MS; however, studies on the safety profile of disease-modifying therapy is limited. There are several studies that show interferon beta 1b to be safe and well tolerated by children and adolescents [16,17]. Although pediatric-onset MS demonstrates similar progression as adult-onset, early identification remains important in managing prognosis of the disease and the psychosocial impact on the patient and family.

Our case was also complicated by the presence of concurrent Lyme disease, a known mimic of multiple sclerosis. Lyme disease is caused by the tick-borne spirochete, *Borrelia burgdorferi*. Lyme disease can include cardiac, dermatologic, rheumatologic, ophthalmic, and neurologic manifestations. In our

patient, a review of systems demonstrated a rash descriptive of erythema chronicum migrans. Serologically, Lyme IgG and IgM titers were elevated, resulting in treatment with intravenous ceftriaxone and subsequent transition to oral doxycycline. Given her rapid improvement in the setting of negative cerebrospinal fluid Lyme titers and culture, the suspicion for disseminated Lyme neuroborreliosis was low. The constellation of her presenting symptoms and brain and spinal cord lesions on MRI were consistent with MS. Lyme neuroborreliosis may present with ocular abnormalities; Correll et al. described 6 pediatric patients who presented with an acquired nystagmus, partial sixth cranial nerve palsy, ptosis, and an Adie's pupil [18,19]. Other ocular manifestations of Lyme disease include follicular conjunctivitis, keratitis, neuroretinitis, and cranial nerve palsies [20]. To date, there is 1 reported case of INO as the presenting symptom of confirmed Lyme neuroborreliosis in an adult [21]. To the best of our knowledge, there have been no reports of INO in the pediatric population attributed to Lyme neuroborreliosis.

Conclusions

In summary, we present a case of pediatric INO as the presenting sign of juvenile-onset multiple sclerosis who also had concurrent Lyme disease. INO is an uncommon ophthalmic finding in the pediatric population and identification may be difficult in the pediatric population. However, when present, a thorough work-up must be performed, including autoimmune, inflammatory, and infectious factors. Early identification of the underlying cause can lead to better outcomes for patients.

Conflict of interest

None.

References:

1. Keane JR: Internuclear ophthalmoplegia: Unusual causes in 114 of 410 patients. *Arch Neurol*, 2005; 62(5): 714–17
2. Steinlin MI, Blaser SI, MacGregor DL, Buncic JR: Eye problems in children with multiple sclerosis. *Pediatr Neurol*, 1995; 12(3): 207–12
3. Leavitt JA, Butrus SI: Internuclear ophthalmoplegia in sickle cell trait. *J Neuroophthalmol*, 1994; 14(1): 49–51
4. Muthukumar N, Veerarajkumar N, Madeswaran K: Bilateral internuclear ophthalmoplegia following mild head injury. *Childs Nerv Syst*, 2001; 17(6): 366–69
5. Rizzo JL, Lloyd M, O'Hara MA: Pediatric internuclear ophthalmoplegia. *J Neuroophthalmol*, 2013; 33(2): 134–36
6. Rismanchi N, Crawford JR: Bilateral internuclear ophthalmoplegia associated with pediatric brain tumor progression: A case series and review of the literature. *J Neurooncol*, 2013; 115(3): 487–91
7. Mazurkiewicz-Beldzinska M, Szmuda M, Zawadzka M: Internuclear ophthalmoplegia as a symptom of ischemic stroke in a girl with patent foramen ovale. *Pediatr Neurol*, 2015; 52(4): 466–67
8. Bodziner RA, Singer W, Hedges TR: Bilateral internuclear ophthalmoplegia in meningoencephalitis. *Dev Med Child Neurol*, 1983; 25(6): 819–20
9. Boiko A, Vorobeychik G, Paty D et al., University of British Columbia MSCN: Early onset multiple sclerosis: A longitudinal study. *Neurology*, 2002; 59(7): 1006–10
10. Duquette P, Murray TJ, Pleines J et al: Multiple sclerosis in childhood: Clinical profile in 125 patients. *J Pediatr*, 1987; 111(3): 359–63
11. Ghezzi A, Deplano V, Faroni J et al: Multiple sclerosis in childhood: Clinical features of 149 cases. *Mult Scler*, 1997; 3(1): 43–46
12. Rieckmann P, Toyka KV, Basseti C et al: Escalating immunotherapy of multiple sclerosis – new aspects and practical application. *J Neurol*, 2004; 251(11): 1329–39
13. Brown JW, Coles A, Horakova D et al: Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA*, 2019; 321(2): 175–87
14. Palace J, Duddy M, Lawton M et al: Assessing the long-term effectiveness of interferon-beta and glatiramer acetate in multiple sclerosis: Final 10-year results from the UK multiple sclerosis risk-sharing scheme. *J Neurol Neurosurg Psychiatry*, 2019; 90(3): 251–60
15. Beiki O, Frumentio P, Bottai M et al: Changes in the risk of reaching multiple sclerosis disability milestones in recent decades: A nationwide population-based cohort study in Sweden. *JAMA Neurol*, 2019; 76(6): 665–71

16. Mikaeloff Y, Moreau T, Debouverie M et al: Interferon-beta treatment in patients with childhood-onset multiple sclerosis. *J Pediatr*, 2001; 139(3): 443–46
17. Adams AB, Tyor WR, Holden KR: Interferon beta-1b and childhood multiple sclerosis. *Pediatr Neurol*, 1999; 21(1): 481–83
18. Correll MH, Datta N, Arvidsson HS et al: Lyme neuroborreliosis: A treatable cause of acute ocular motor disturbances in children. *Br J Ophthalmol*, 2015; 99(10): 1401–4
19. Stricker RB, Winger EE: Holmes-Adie syndrome and Lyme disease. *Lancet*, 2001; 357(9258): 805
20. Lesser RL: Ocular manifestations of Lyme disease. *Am J Med*, 1995; 98(4A): 605–625
21. Hardon WJ, Bensen HJ, van Nouhuys-Leenders J, Mulder B: Internuclear ophthalmoplegia as the first sign of neuroborreliosis. *J Neurol*, 2002; 249(8): 1119–20