

# Etiology and Clinical Features of Optic Neuritis in Two Children: A Case Report

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**Background:** Optic neuritis (ON) is inflammation of the optic nerve that can occur in both adults and children. This disease is marked by a heterogeneous presentation in children and has clinical and epidemiologic characteristics that differ greatly from those found in adults. The purpose of this report is to illustrate the clinical features of ON that occur during childhood and to highlight the differences of ON in children versus adults. In doing so, we aim to add to the sparse current literature on this topic and help prevent the future misdiagnosis of ON in pediatric patients.

**Case Presentations:** An 11-year-old female presented with bilateral decreased visual acuity and significant ocular pain. The ophthalmic presentation and diagnostic workup led to the diagnosis of acute disseminated encephalomyelitis with ON. A second patient, a 12-year-old male, presented with decreased visual acuity and bilateral papilledema. Alongside a diagnosis of bilateral ON, a muscle biopsy confirmed mitochondrial cytopathy as the etiology of his presenting symptoms.

**Conclusions:** ON in children may be related to specific infections, autoimmune disorders, diseases of adjacent anatomical structures, or demyelinating disorders. Attacks may be acute or subacute with signs of reduced visual acuity, abnormal pupillary response, loss of color vision, impaired contrast sensitivity, and decreased peripheral vision. Awareness of this complex disease allows the clinician to initiate specific treatment and follow-up care that may reduce subsequent morbidity and the rate of recurrence.

**Keywords:** optic neuritis; diagnosis; clinical features; pediatric; case report

## INTRODUCTION

**O**ptic neuritis (ON) is inflammation of the optic nerve that can affect patients at any age, including infancy. The disease is more common in adults with an incidence estimate of 1–2 per 100,000 people.<sup>1</sup> In contrast, the annual incidence of pediatric ON is only 0.15–0.57 per 100,000 people.<sup>2–4</sup> Although relatively rare in children, pediatricians and primary care clinicians should be aware of the specific features of pediatric ON in order to facilitate diagnostic testing and avoid misdiagnoses. Pediatric ON is usually associated with a good prognosis. However, a minority of children (22% in one study) will have persistent visual loss.<sup>4</sup> Knowledge regarding the clinical features, treatment, prognosis, and future neurologic implications of ON in children has grown significantly over the past decade.<sup>5</sup> These studies have shown that pediatric ON is a distinct clinical entity when compared to ON in adults.<sup>3</sup> Bilateral involvement, optic disc edema, and vision loss are more commonly seen in pediatric cases of ON when compared with adult cases of

ON. Furthermore, orbital pain is less frequently reported in pediatric cases than in adult cases.<sup>1</sup> Since ON is a clinical diagnosis based on the history and physical examination findings, it is crucial for clinicians to be aware of these important clinical differences. This article presents two cases of ON in children with very different etiologies and highlights recent studies focused on the epidemiology and clinical features of pediatric ON.

## CASE PRESENTATIONS

**Case 1:** An 11-year-old female in good general health presented to the emergency department (ED) with a complaint of viral symptoms that began 1 month earlier. There was no significant family history, chronic illness, or recent vaccinations. Her symptoms included headache, body aches, decreased visual acuity, eye pain, and fatigue. Gradually, most of her symptoms resolved, except for the eye pain and decreased visual acuity. Her ocular examination displayed hippus, blurred optic discs

bilaterally, and enlarged retinal vessels. Visual acuity was 20/800 in her right eye and 20/200 in her left. A relative afferent pupillary defect (RAPD) was observed in the right eye. On hospital admission, color vision (ishihara) was severely impaired in both eyes. Ocular movements were full range but associated with pain. Visual fields were intact. No conjunctival congestion or lid swelling was noticed. The anterior segments of both eyes was normal. The remaining sections of systemic and neurological examination were normal. Magnetic resonance imaging (MRI) of the orbits showed normal fibers within the orbits and in the optic nerves, but it also revealed abnormal fibers outside the orbits. A lumbar puncture was performed, which had a normal opening pressure of 22 cm. Cerebrospinal fluid (CSF) studies were negative, including bacterial and viral cultures, mycoplasma and viral serologies, antistreptolysin O titer, antinuclear antibody panel, C-reactive protein, and rheumatoid factor. The diagnosis of bilateral ON was made. The patient's symptoms improved over 5 days of intravenous methylprednisolone (30 mg/kg per day), and she was discharged home with the diagnosis of acute disseminated encephalomyelitis with ON. At her three-month follow up, she had full visual recovery. One year later, the patient again developed symptoms of eye pain and decreased visual acuity. Repeat MRI indicated persistent areas of demyelination of the optic chiasm and pre-chiasmatic optic nerves. This was consistent with recurrent ON, which responded to steroids again. Due to the recurrence of the ON, the patient was referred for evaluation for multiple sclerosis (MS).

Case 2: A 12-year-old male presented to the ED with a history of 1 week of decreased vision in his right eye followed by decreasing vision in his left eye. There were no similar complaints in his past medical history. He also had no history of fever, symptoms of upper respiratory tract infection, recent vaccinations, bleeding tendencies, or trauma. His physical examination was significant for pain with lateral eye movements. The patient was unable to visualize symbols that were greater than 3 inches away. Color vision and red desaturation were reduced in both eyes. Visual field assessment was not performed because the patient grew restless. RAPDs were documented in both eyes. Fundoscopic examination with dilation revealed a loss of the optic discs in both eyes with 1- 2+ edema bilaterally. No conjunctival congestion or lid swelling was noticed. The anterior segments of both eyes were normal. The remainder of the systemic and neurological examination was normal. A lumbar

puncture was performed, and it showed a normal opening pressure of 18 cm. Inpatient CSF studies (IgE, glucose, lactic acid, and electrophoresis for oligoclonal bands), CSF cultures, and Complete Blood Count (CBC) were all found to be normal. An MRI was obtained and found to be unremarkable. Amino acid studies revealed elevations of alanine and proline, which was concerning for primary lactic acidemia. The patient was started on intravenous methylprednisolone for 5 days (30 mg/kg per day) for presumed ON. This was followed by an oral corticosteroid taper over 2 weeks. A subsequent muscle biopsy showed significantly reduced activity of complex I and mildly reduced activity of complexes III and IV of the electron transport chain. This was consistent with Leber Hereditary Optic Neuropathy with associated bilateral ON. The patient was discharged on a mitochondrial cocktail of coenzyme Q10, thiamine, riboflavin, and carnitine. At his one-year follow-up, the patient had maintained his vision and his neurological examination was normal.

## DISCUSSION

ON is a relatively rare condition in children, which can cause mild to severe vision loss. As demonstrated in these two cases, early recognition is important for diagnosis and prompt treatment. The diagnosis includes a wide range of inflammatory and demyelinating conditions associated with optic neuropathy (Table 1). ON can present in isolation or be the first manifestation of a chronic demyelinating illness, such as MS or neuromyelitis optica.<sup>5</sup> Secondary causes of ON are protean and include infections, diseases of the adjacent sinuses or orbital structures, trauma, vascular insufficiency, metastases, toxins, or nutritional deficiencies.<sup>6-11</sup> The exact pathogenesis of ON is not well understood. It is likely due to a delayed type IV hypersensitivity reaction induced by cytokines and other inflammatory mediators released from activated peripheral T-cells, which cross the blood-brain barrier and cause an autoimmune reaction.<sup>4-7,13</sup> However, the specific mechanism and target antigen(s) remain unknown. In many cases, direct injury to the axon may also play a role in the pathophysiology.<sup>13</sup> Emerging case reports indicate that COVID-19 is a rare, but potential cause of ON in both children and adults.<sup>11,14,15</sup> While the exact link between COVID-19 and ON is still under study, proposed mechanisms behind its pathogenesis include direct viral invasion, blood-brain barrier disruption, cytokine storm, autoimmunity, and coagulopathy.<sup>16-18</sup>

**Table 1.** Noninfectious etiologies of optic neuritis.<sup>6-12</sup>

Demyelinating diseases	Autoimmune	Drugs and chemicals	Miscellaneous
Multiple sclerosis	Sarcoidosis	Lead	Systemic vasculitis
Idiopathic inflammatory demyelination	Systemic lupus erythematosus	Methanol	Diabetes
Neuromyelitis optica	Sjögren's syndrome	Quinine	Vitamin A, B12 deficiencies
Acute disseminated encephalomyelitis	Behçet's disease	Arsenic	Tumor metastasis
Myelin oligodendrocyte glycoprotein autoantibody disease	Graves ophthalmopathy	Ethambutol	Bee and wasp stings
Hereditary neuropathies		Antibiotics	Leukemia
			Vaccination
			Sinusitis
			Sickle cell
			Trauma

Rapid determination of the underlying cause of ON is vital for implementing both timely and appropriate treatment in a child with acute vision loss. As seen in both cases described in this report, a diagnostic workup may require laboratory investigations and neuroimaging that extend beyond a simple history and ophthalmologic examination. Differentiating between various causes of ON may require serologic testing, CSF analysis and cultures, visual field perimetry, muscle biopsy, optical coherence tomography, or gadolinium-enhanced MRI of the brain and orbits.<sup>6</sup> Although MRI is not required to diagnose ON in children, it is the best imaging technique to confirm the diagnosis of acute demyelinating ON. One investigator has recommended that 'all children with ON should undergo neuroimaging not only to evaluate for other signs of demyelinating disease, but also to exclude the possibility of an intracranial lesion'.<sup>4</sup> Recent research in biomarkers, such as aquaporin-4 and myelin oligodendrocyte glycoprotein, may also be helpful in differentiating between infectious and autoimmune disease.<sup>9,19</sup> This information can then be used in counseling patients and their families about the disease, prognosis, and risk of recurrence.

Much of what we know about ON in childhood is based upon limited case series and retrospective reviews.<sup>19,20</sup> To date, there are no prospective clinical trials or published guidelines for children. Additionally, most early reports of pediatric ON focused on children older than 12 years of age.<sup>20</sup> However, it is generally accepted that pediatric ON has very different clinical features when compared to those found in adults (Table 2). For example, while the most common cause of ON in adults is demyelination, post-infectious or

post-vaccination inflammation represents most cases of pediatric ON.<sup>12,20,21</sup> This was evident in our first case where ON was preceded by a viral syndrome. In general, these children will not require expensive laboratory studies, such as a lumbar puncture or an MRI, to make a diagnosis of ON.<sup>22</sup> Instead, a careful history should be aimed at detecting recent infections, vaccinations, or presence of vasculitis. In contrast with the adult presentation of ON, children are more likely to have bilateral disease, anterior optic nerve involvement with papillitis, and more severe vision loss on initial presentation.<sup>21</sup> Young children may not notice unilateral vision loss and may casually accept bilateral vision loss until it becomes incapacitating.<sup>8</sup> Eye pain, which is associated with ocular movements and may precede or coincide with the visual symptoms, occurs in more than 90% of adults.<sup>21</sup> Observational studies in children have demonstrated the absence of periocular pain in over half of cases in their pediatric study population.<sup>21</sup> However, both cases presented here did have eye movements associated with pain.

**Table 2.** Infectious etiologies of optic neuritis.<sup>6-12</sup>

Herpes Zoster	COVID-19
Borrelia	Rubella
Syphilis	Cytomegalovirus
Tuberculosis	Toxocariasis and helminths
Toxoplasmosis	Flavivirus
Leptospirosis	Adenovirus
Mononucleosis	Coxsackievirus
Brucella	Bartonella
Pertussis	Streptococcus
Varicella	

**Table 3.** Optic neuritis in adults versus children.<sup>1,4,7,8,11,12,14,15</sup>

Adult	Pediatric
1–2 per 100,00 incidence	0.15–0.57 per 100,00 incidence
Mean age 31.8 years	Mean age 9.5 years
Most common cause is demyelination	Most often postinfectious or postimmunization
Pain with eye movements (90%)	Headache (53%)
Unilateral disease (70%)	Bilateral disease (72%)
Visual acuity <20/200 (36%)	Visual acuity <20/200 (90–95%)
Female preponderance 2:1	Female preponderance 1:1 prepuberty
Optic disc swelling or papillitis (35%)	Optic disc swelling or papillitis (64–87%)
Retrobulbar (65%)	Retrobulbar (13–36%)
Risk of multiple sclerosis 38%	Risk of multiple sclerosis 10–29%
Visual recovery (>20/40) 90–95%	Visual recovery (>20/40) 80–89%

A careful ophthalmologic examination may help to differentiate a typical presentation of ON from atypical cases (Table 3). Vision loss occurs over a period of hours to days, peaking within several weeks of symptom onset.<sup>12</sup> In our patients, dyschromatopsia or color desaturation, was found to be a sensitive sign of acute ON.<sup>12</sup> Ishihara color plates were used to assess red color desaturation. However, if these plates are unavailable, simply ask the patient to compare the color of a bright red object with each eye. Furthermore, physicians should assess contrast sensitivity by shining a light in each eye and asking the patients to compare the brightness. A useful technique is to ask, 'If I were to give you a dollar for this brightness' (shine light in normal eye), 'How much would you give me for this ...?' (shine light in affected eye). Lastly, physicians ought to perform a confrontational visual field test, specifically looking for central or paracentral scotomas.<sup>23</sup> It may be helpful to say to children, 'If what you see is like a television screen, then where is the part that is missing?' Scotomas typically occur over the course of a few hours to days, with maximum defects reached within several days.<sup>23</sup>

Both patients had dilated fundoscopic examinations performed to avoid missing other retinal diseases that could be mistaken for ON, such as retinal detachment. Before dilating the pupils, determine the presence or absence of a RAPD. This can be demonstrated with the swinging flashlight test, which is performed by moving a penlight back and forth between the eyes. The afferent pupillary defect becomes obvious when stimulation of the normal eye elicits a brisk constriction of both pupils, while stimulation of the diseased eye causes dilation of both pupils. Note that in bilateral involvement, the RAPD may not be apparent. One observational study of

ON in children reported the presence of color vision defects in 50% of children, visual field defects in 58.5%, and RAPD in 67%.<sup>24</sup> The most important fundoscopic finding in ON is the presence of optic disc edema, known as papillitis. Most children with ON have optic disc edema, where as with only 35% of adults with ON present in this manner.<sup>18</sup> This was documented in both of our patients. However, optic disc edema can be difficult to visualize in a fidgeting child. In addition to blurred disc margins, look for optic disc pallor, filling-in of the physiological disc cup, elevation of the optic disc, distended retinal veins, and dilated disc capillaries. Of these features, evidence of thickening of the peripapillary nerve fiber layer was found to provide the highest level of accuracy as a single sign of optic disc edema.<sup>25</sup> Ocular point-of-care ultrasound can also enable pediatricians to detect optic disc elevation and abnormal optic nerve sheath diameter at the bedside, thereby expediting the diagnosis of ON.<sup>26</sup>

Fortunately, both patients had none of the signs and symptoms that might indicate a more serious pathology. Hemorrhages of the nerve fiber layer, detectable by fundoscopic examination, are rare in children with ON and should prompt an investigation to exclude other diagnoses. Additional clinical features that indicate a more serious pathology include insidious onset, progressive visual loss for more than 2 weeks, painless visual loss, severe optic nerve pallor at presentation, marked uveitis or retinal periphlebitis, slow visual recovery, ongoing neurologic symptoms, and any deterioration after withdrawal of steroids.<sup>10,23</sup> These clinical red flags require careful diagnostic assessment of other diseases that are associated with optic neuropathy (Table 4). However, subclinical or spontaneously resolving disease

**Table 4.** Clinical features of pediatric optic neuritis.<sup>1-7,12,13,23</sup>

- Preceding viral illness or febrile prodrome
- Acute or subacute visual loss in one or both eyes
- Progressive over days to several weeks
- Photopsias precipitated with eye movement
- Abnormal color vision (notably red color desaturation)
- Reduced contrast sensitivity
- Visual field defect (central or paracentral scotomas)
- Periocular pain and pain with eye movement
- Relative afferent pupillary defect (Marcus Gunn pupil)
- Normal (retrobulbar) or swollen optic disc (papillitis)
- Normal macula and peripheral retina
- Uveitis or retinal periphlebitis possible

states, atypical symptoms, recurrent isolated attacks, and a poor history provided by young children can make diagnosis of ON challenging. In response to this diagnostic complexity, Yeh and colleagues have created a comprehensive algorithm for the approach to a child presenting with acute ON.<sup>5</sup> This approach was utilized in our patients and consisted of an ophthalmologic examination, lumbar puncture, MRI of the brain, and a broad rheumatologic workup.

The first patient described here was referred for a MS workup after a recurrent episode of ON. MS is an immune-mediated demyelinating disorder that attacks myelinated axons in the central nervous system, which leads to significant physical disability.<sup>10</sup> The relationship between an initial episode of ON and the development of MS has been established by many previous studies, none of which are prospective. The reported risk varies greatly from 13 to 36% of children.<sup>5</sup> Lucchinetti et al studied childhood ON and estimated the risk of MS to be 13% by 10 years of age, 19% by 20 years of age, 22% by 30 years of age, and 26% by 40 years of age.<sup>27</sup> A meta-analysis by Waldman et al showed that for every one year increase in age, the odds of a child developing MS after an initial episode of ON increased by 32%.<sup>28</sup> In addition, the risk of progression to MS was markedly increased (27-fold) with the presence of demyelinating lesions on brain MRI scans. Other reported risk factors for MS include racial or geographic factors, female gender, and recurrent ON.<sup>24,29</sup> However, prospective studies are necessary to support these findings and address the conflicting data concerning pediatric ON.

Treatment of ON is aimed at identifying and treating the underlying cause of the condition. However, even without treatment, it was observed that 80% of children spontaneously recovered their vision within 2–3 weeks.<sup>24</sup> Even if a

child's vision does recover, pediatric eyes may retain some functional defects in visual fields, low-contrast vision, and color perception.<sup>30</sup> ON treatment guidelines are based on large-scale studies in adult patients and a preferred protocol has been developed from the optic neuritis treatment trial (ONTT).<sup>1</sup> These treatments often include intravenous methylprednisolone (4–30 mg/kg per day) for 3–5 days followed by an oral corticosteroid tapered over 2 weeks.<sup>24,29</sup> Both patients presented here were initially treated with IV methylprednisolone (30 mg/kg per day), with differing subsequent treatment due to the varying pathologies and causes of their ON. Physicians will likely tailor their decision to treat based on age, gender, laterality, and level of visual acuity. If initial treatment with steroids is not successful, additional treatment options include a second round of intravenous steroids, intravenous immunoglobulin, or plasma exchange.<sup>29</sup> Factors that may predict a poor recovery in children include age over 10 years old, profound loss of visual acuity at presentation, optic atrophy, a diagnosis of MS, and bilateral involvement at presentation.<sup>30-32</sup> Both children presented here were over 10 years old and presented with severely decreased visual acuity bilaterally. Although they initially recovered, the first child was referred for evaluation for MS.

## CONCLUSIONS

ON is a complex and challenging disease in children. It has specific clinical epidemiologic characteristics that differ from those found in adults. Blurred vision and headache may be the first and only presenting symptoms of a systemic disease, such as MS, serious infection, or an underlying mitochondrial abnormality. In the two cases presented here, early recognition of the disease was made after a thorough ophthalmologic examination, CSF analysis, MRI imaging, and rheumatologic studies. Prompt diagnosis of this complex disease allows clinicians to initiate corticosteroids and arrange follow-up care that may reduce subsequent morbidity in this vulnerable population.

## Conflict of interest and funding

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