Longitudinally Extensive Optic Neuritis in Pediatric Patients

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Abstract

Extensive optic nerve demyelinating lesions on magnetic resonance imaging (MRI) in adults could indicate a diagnosis other than multiple sclerosis with worse prognosis such as neuromyelitis optica. We report the frequency of longitudinally extensive lesions in children with first events of optic neuritis. Subjects had brain or orbit MRI within 3 months of onset and were evaluated at the University of California, San Francisco, Pediatric Multiple Sclerosis Center. Lesion length, determined by T2 hyperintensity or contrast enhancement, was blindly graded as absent, focal or longitudinally extensive (at least 2 contiguous segments of optic nerve). Of 25 subjects, 9 (36%) had longitudinally extensive optic neuritis. Extensive lesions were not associated with non–multiple sclerosis versus multiple sclerosis diagnosis (P = 1.00). No association between age and lesion extent was observed (P = .26). Prospective studies are needed to determine if longitudinally extensive optic neuritis can predict visual outcome.

Keywords

optic neuritis, multiple sclerosis, neuromyelitis optica, MRI

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Optic neuritis can be a presenting symptom of various inflammatory conditions. The majority of cases demonstrate abnormal T2 signal and gadolinium enhancement of the optic nerve on magnetic resonance imaging (MRI). The most common form, acute demyelinating optic neuritis, is frequently associated with multiple sclerosis in adults. Idiopathic and postinfectious optic neuritis are more common in pediatric patients, but multiple sclerosis is still the most frequent chronic neuroimmunologic disorder associated with optic neuritis.1-3 Less often in adults or children, optic neuritis is associated with neuromyelitis optica, sarcoidosis, and other autoimmune conditions. These conditions can carry a worse visual prognosis than multiple sclerosis–related optic neuritis and can require prolonged immunosuppression.1-9 Early diagnosis in these conditions can be paramount for vision preservation by allowing for more aggressive initial treatments.

One of the first tests performed on patients with optic neuritis is MRI of the brain and/or orbits. The importance of optic nerve lesion length on this initial MRI is unclear. Recent studies in adults have suggested that predominant involvement of more posterior components of the visual pathway can be more associated with a diagnosis of neuromyelitis optica than multiple sclerosis.10,11 These studies conflict as to whether lesion length predicts neuromyelitis optica.10,11 Extensive spinal cord lesions predict neuromyelitis optica in adults.12 In children, this association is less certain, with reported low frequencies of neuromyelitis optica antibodies in children with extensive cord lesions.13-15 With respect to lesion length and visual outcomes, there are also discrepancies across studies, but multiple studies suggest a potential for worse outcome with larger lesions.16-18 In pediatric patients, age can confound the radiographic presentation of optic neuritis. Younger pediatric patients with multiple sclerosis often have larger T2-bright changes on their initial brain MRI scans.19 Similarly, age has been associated with bilateral optic nerve involvement.3 Although bilateral optic neuritis is more commonly associated with neuromyelitis optica than multiple sclerosis in adults, the reverse is seen in children.1

Our aims were to define longitudinally extensive optic neuritis in children and determine its frequency in a population of patients presenting with a first optic neuritis to a multiple sclerosis center for diagnosis. We further sought to address whether age is associated with optic neuritis extent.
Methods

Participants

Our study was approved by the Committee for Human Research at the University of California, San Francisco. Participants were identified by chart review of all patients evaluated at the University of California, San Francisco, Pediatric Multiple Sclerosis Center since inception (2006-2012). Subjects were selected who had first neurologic episodes of clinical optic neuritis. Inclusion criteria were age 0 to 18 years at symptom onset, presentation consistent with clinical optic neuritis (subacute onset of visual complaints, retro-orbital discomfort or pain with eye movements for >24 hours; documented acuity, visual field or color loss, or afferent pupillary defect) and MRI imaging within 3 months of symptom onset that allowed adequate evaluation of the optic nerves. They must have been prospectively followed until a definitive diagnosis was made (multiple sclerosis, neuromyelitis optica, or other disease). Patients were excluded who already had a known underlying neuroimmunologic diagnosis at optic neuritis onset, whose symptoms resolved within 24 hours and who had an alternative ophthalmic diagnosis for visual loss such as eye trauma or tumor.

Measures

Participant charts were reviewed for abstraction of demographic and clinical data. Multiple sclerosis and neuromyelitis optica diagnoses were based on published criteria, including the use of aquaporin-4 antibody testing and cerebrospinal fluid testing. Other diagnoses required the reasonable exclusion of multiple sclerosis and neuromyelitis optica and additional data to support the alternative diagnosis. High-contrast near card visual acuity (with refractive correction as needed) was measured for each eye of all patients. Follow-up acuity measurements were selected from time points before the onset of any additional episodes of clinical optic neuritis.

Clinical brain MRI scans obtained on scanners (1-Tesla to 3-Tesla) within and outside University of California, San Francisco, were reviewed by 2 blinded neuroradiologists (BPS, CPH) who reviewed scans independently and then resolved differences by consensus. Optic nerve abnormalities of either T2 signal hyperintensity or contrast enhancement were scored as not present, focal, or longitudinal, defined as involving 2 or more contiguous optic nerve segments (anterior orbital, posterior orbital, canalicular, or cisternal). If T2 hyperintensity was extensive, but enhancement focal, the lesion was still considered extensive. Chiasm involvement was also noted.

The presence or absence of longitudinally extensive optic neuritis and final diagnosis (multiple sclerosis vs non–multiple sclerosis) were treated as dichotomous variables. Characteristics of those with and without extensive optic neuritis were compared using the Fisher exact test for categorical variables and Student t test for mean age. To evaluate the association of lesion extent with final neuroimmunologic diagnosis, Fisher exact test was used. Analyses were performed with Stata 12.0 software (StataCorp, College Station, Texas). A 2-sided P value of .05 was considered significant.

Results

Of 292 patients screened, 36 met clinical inclusion criteria. Of these, 25 had interpretable images of the optic nerves (17 with dedicated MRI sequences of the orbits). Longitudinally extensive optic neuritis was identified in 9 (36%) of these 25 participants (Figure 1). A non–multiple sclerosis diagnosis had ultimately been made in 5 (20%) participants. Characteristics of subjects with and without extensive optic neuritis are summarized in Table 1. Although mean age was lower in those with longitudinally extensive optic neuritis, this did not reach statistical significance (P = .26).

Chiasm involvement was seen in 4 of 20 relapsing-remitting multiple sclerosis cases and 1 of 2 neuromyelitis optica cases. The single patient with longitudinally extensive optic neuritis and chiasm involvement had relapsing-remitting multiple sclerosis. Bilateral optic neuritis was observed only in participants with relapsing remitting multiple sclerosis and was seen in younger, less than 11 years (n = 3 of 7), and older subjects (n = 5 of 13).
Additional clinical episode of optic neuritis. We have introduced a definition of longitudinally extensive optic neuritis, which is a demyelinating disease of the optic nerve that includes contiguous involvement. The majority of patients in our study experienced return to normal high-contrast near vision. Limitations of the study inherent to the retrospective data collection, including heterogeneous examinations from outside providers at symptom onset and nonuniform timing of follow-up visits, prevented the systematic evaluation of initial severity of vision loss and lesion extent as well as time to recovery. Future studies would also benefit from more sensitive measures of visual loss such as low-contrast vision testing and measures of optic nerve axonal loss such as optical coherence tomography.

Referral bias is a potential concern, though pediatric neuroimmunologic disease, even if “typical,” is rare and consultation from a specialized center is frequently sought. We suspect milder optic neuritis cases can be underrepresented as they can come to a physician’s attention later. We have not addressed the frequency of longitudinally extensive lesions among cases of idiopathic optic neuritis, as our inclusion criteria required a non–multiple sclerosis diagnosis. We found no association between lesion extent and non–multiple sclerosis diagnoses such as neuromyelitis optica, but the confidence interval is too wide to be conclusive. Given the frequency of extensive optic nerve lesions in our sample of subjects with relapsing remitting multiple sclerosis and that multiple sclerosis is more common than other diagnoses, lesion extent might not be a satisfactory criterion for predicting neuromyelitis optica or other non–multiple sclerosis diagnoses in children with first optic neuritis events.

Lesion extent can be a factor of age, as has been shown for bilateral optic neuritis and brain lesions in younger pediatric patients. However, we did not find a statistically significant association of age with longitudinally extensive lesions.

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The definition of longitudinally extensive optic neuritis provides a basis on which to study lesion size and risk factors for poor visual outcomes. Future studies in larger, prospective cohorts can clarify whether lesion length is associated with worse visual prognosis. We observed longitudinally extensive lesions in one-third of patients with first optic neuritis episodes who ultimately received underlying diagnoses at a multiple sclerosis specialty center. Refinement of this definition of longitudinally extensive optic neuritis could be pursued with prospectively collected, uniform MRI protocols, but the imaging used in this study reflects the brain and orbital MRIs typically used by practicing physicians to make treatment choices.

One-third of patients ultimately diagnosed with relapsing remitting multiple sclerosis had presented with longitudinally extensive optic neuritis. We found no association between lesion extent and non–multiple sclerosis diagnoses such as neuromyelitis optica, but the confidence interval is too wide to be conclusive. Given the frequency of extensive optic nerve lesions in our sample of subjects with relapsing remitting multiple sclerosis and that multiple sclerosis is more common than other diagnoses, lesion extent might not be a satisfactory criterion for predicting neuromyelitis optica or other non–multiple sclerosis diagnoses in children with first optic neuritis events.

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The definition of longitudinally extensive optic neuritis provides a basis on which to study lesion size and risk factors for poor visual outcomes. Future studies in larger, prospective cohorts can clarify whether lesion length is associated with visual prognosis in pediatric optic neuritis and whether known genetic or environmental risk factors for demyelinating disease affect lesion size and severity.

### Table 1. Characteristics of Patients With and Without Longitudinally Extensive Optic Neuritis at Disease Onset.

<table>
<thead>
<tr>
<th></th>
<th>LEON present</th>
<th>LEON absent</th>
<th>P value</th>
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<tbody>
<tr>
<td>Number of patients (%)</td>
<td>9 (36)</td>
<td>16 (64)</td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>0 (0)</td>
<td>3 (19)</td>
<td>.28</td>
</tr>
<tr>
<td>Ethnicity and race (%)</td>
<td>3 (38)</td>
<td>4 (27)</td>
<td>.66</td>
</tr>
<tr>
<td>Mean age in years at onset (SD)</td>
<td>9.8 (4.5)</td>
<td>11.8 (4.0)</td>
<td>.26</td>
</tr>
<tr>
<td>Patients &lt;11 y old (%)</td>
<td>5 (56)</td>
<td>6 (38)</td>
<td>.43</td>
</tr>
<tr>
<td>Bilateral symptoms (%)</td>
<td>2 (22)</td>
<td>6 (38)</td>
<td>.66</td>
</tr>
<tr>
<td>Chiasm involved (%)</td>
<td>1 (11%)</td>
<td>4 (25%)</td>
<td>.62</td>
</tr>
<tr>
<td>Final diagnosis not MS* (%)</td>
<td>2 (22%)</td>
<td>3 (19%)</td>
<td>1.00</td>
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Abbreviations: LEON, longitudinally extensive optic neuritis; MS, multiple sclerosis; SD, standard deviation; WNH, white non-Hispanic.

*The absence of extensive lesions included those with focal and absent T2 hyperintensity or contrast enhancement of the optic nerve.

Fisher exact test except test for mean age and rank sum for median age.

Ethnicity and race information missing for 3 patients.

Non–multiple sclerosis diagnoses included neuromyelitis optica, neurosarcoidosis, and chronic relapsing inflammatory optic neuritis.

We did not find an association between longitudinally extensive optic neuritis and a non–multiple sclerosis diagnosis (P = 1.00). In the longitudinally extensive optic neuritis group, 7 subjects (78%) were diagnosed with relapsing-remitting multiple sclerosis and 1 with chronic relapsing inflammatory optic neuritis (with a normal brain MRI), and 1 was treated for suspected neurosarcoidosis versus vasculitis after exclusion of multiple sclerosis and neuromyelitis optica. In those without extensive lesions, 13 (81%) had relapsing-remitting multiple sclerosis, 2 had neuromyelitis optica, and 1 had neurosarcoidosis. Of those with relapsing-remitting multiple sclerosis, 35% had longitudinally extensive optic nerve lesions at presentation.

Given that vision examinations were made in different settings before referral to the pediatric multiple sclerosis center, consistent and uniform visual function measures were limited to follow-up near card high contrast acuity. For 22 of the 25 patients (88%), follow-up Snellen equivalent visual acuity in each eye was 20/20 (J1). Of the remaining 3 patients, one with multiple sclerosis had visual acuity equivalent of 20/30 in the affected eye at greater than 1 year of follow-up. Longitudinally extensive optic neuritis had been present in the ipsilateral optic nerve. A patient with neuromyelitis optica had follow-up acuity measurement of Snellen equivalent 20/40-2 in an affected eye without an extensive lesion, but this data was from a visit only 3 months following onset of symptoms. The patient with chronic relapsing inflammatory optic neuritis had a visual acuity equivalent of 20/200 (in eye with longitudinally extensive lesion) at 8 weeks of follow-up before having an additional clinical episode of optic neuritis.

### Discussion

We have introduced a definition of longitudinally extensive optic neuritis in pediatric patients and demonstrated that although lesion extent may not be a satisfactory tool to distinguish a nonmultiple sclerosis versus multiple sclerosis diagnosis in children, it can hold importance for future studies of visual prognosis. Our definition requires contiguous involvement in at least 2 of 4 segments of the optic nerve and is based on prior studies that suggest lesions at least one-third the length of the adult optic nerve can be associated with worse visual prognosis. We observed longitudinally extensive lesions in one-third of patients with first optic neuritis episodes who ultimately received underlying diagnoses at a multiple sclerosis specialty center. Refinement of this definition of longitudinally extensive optic neuritis could be pursued with prospectively collected, uniform MRI protocols, but the imaging used in this study reflects the brain and orbital MRIs typically used by practicing physicians to make treatment choices.

One-third of patients ultimately diagnosed with relapsing remitting multiple sclerosis had presented with longitudinally extensive optic neuritis. We found no association between lesion extent and non–multiple sclerosis diagnoses such as neuromyelitis optica, but the confidence interval is too wide to be conclusive. Given the frequency of extensive optic nerve lesions in our sample of subjects with relapsing remitting multiple sclerosis and that multiple sclerosis is more common than other diagnoses, lesion extent might not be a satisfactory criterion for predicting neuromyelitis optica or other non–multiple sclerosis diagnoses in children with first optic neuritis events.

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Author Contributions
JG, VK, BPS, and CPH contributed to data collection. JG analyzed the data and along with EW interpreted the data. Further, JG completed the first draft of the article. All authors took part in designing the study and revising the manuscript.

Authors' Note
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