Title

The Pediatric Optic Neuritis Prospective Outcomes Study: Two-Year Results.

Journal

Ophthalmology, 129(8)

Authors

Pineles, Stacy
Henderson, Robert
Repka, Michael
et al.

Publication Date

2022-08-01

DOI

10.1016/j.ophtha.2022.03.021

Peer reviewed

Published in final edited form as:

J Neuroophthalmol. 2016 June ; 36(2): 115–117. doi:10.1097/WNO.0000000000000360.

Pediatric Optic Neuritis Prospective Outcomes Study

Stacy L. Pineles, MD, **Grant T. Liu, MD**, **Amy T. Waldman, MD**, **Elizabeth Lazar, MS, MPH**, **Mark J. Kupersmith, MD**, **Michael X. Repka, MD, MBA**, and **Pediatric Eye Disease Investigator Group and the Neuro-Ophthalmology Research Disease Investigator Consortium**

Jaeb Center for Health Research, Tampa, Florida.

Optic neuritis (ON) is a well-studied disorder of the optic nerve in adults (1). The Optic Neuritis Treatment Trial (ONTT) is one of the most widely cited clinical trials in ophthalmology and provided invaluable knowledge regarding the etiology, management, prognosis of ON, and subsequent diagnosis of multiple sclerosis (MS) in affected adults. However, there is little prospective data related to ON in children (2).

The pathogenesis of pediatric optic neuritis (PON) is not well understood. Our understanding about causation, natural history, response to therapy, and prognosis is based on case reports and retrospective case series, in addition to generalization from adult data (3–8). There are differences between adult ON and PON that may impact response to treatment, visual recovery and subsequent diagnosis of MS. First, children often experience greater visual acuity deficits and are more likely to develop bilateral eye involvement than adults (1). In addition, a greater percentage of children present with optic disc edema. Although optic disc swelling was found to be protective in adults with ON (9), its implications for children are not known. A meta-analysis of patients with PON revealed that the risk of subsequently developing MS was higher in children who were older and in those who presented with white matter lesions on magnetic resonance imaging (MRI) (10). However, a meta-analysis could not draw definitive conclusions regarding the natural history or provide evidence that treatment was beneficial. Other recent retrospective studies have described the extent of visual acuity recovery after an episode of ON (8), but have not prospectively evaluated the association with MS or other systemic diseases. Furthermore, no studies have systematically and prospectively evaluated other outcome measures such as low-contrast visual acuity, retinal nerve fiber layer thickness, or quality of life in children with PON.

In addition to the lack of data on the presentation and natural history of PON, guidelines for optimal treatment are unavailable. In the 1950s, corticosteroids were used to treat demyelinating diseases including ON and MS in adults and children. The results from the ONTT have modified evaluation, treatment, and outcomes of demyelinating diseases in adults, providing evidence-based management of these patients (11). The study demonstrated that the administration of intravenous corticosteroids hastens visual recovery

Address correspondence to Stacy L. Pineles, MD, Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647; pedig@jaeb.org.

in adults, but did not affect the long-term visual or neurologic prognosis (9,12,13). Furthermore, the ONTT showed that initial treatment with oral corticosteroids was associated with an increased risk of relapse of ON; however, the relationship between treatment and risk of relapse remains unclear (13). Moreover, intravenous corticosteroids did not prevent optic nerve atrophy (14) and may be harmful with regard to the risk of developing MS in the long-term (15). Although ONTT did not include children and there are no similar data for PON, intravenous corticosteroids have remained the mainstay of treatment for PON.

In a recent survey, 86% of physicians believed that not all acute attacks of central nervous system (CNS) demyelinating diseases require treatment (16). A survey involving a hypothetical treatment trial of PON revealed that 98% of the 49 ophthalmologists, neurologists, and eye professionals queried would enroll their pediatric patients into such a trial (16). These findings support the need for studies to provide evidence-based care of PON.

To confirm the benefit or futility of corticosteroids for PON and to establish appropriate treatment guidelines, a randomized, placebo-controlled trial of the effects of corticosteroids in pediatric participants with acute optic neuritis—Pediatric Optic Neuritis Treatment Trial (PONTT)—is needed. However, because clinical trials of uncommon diseases may have difficulty with enrollment and the incidence of PON is low, we are launching a pilot study. The Pediatric Optic Neuritis Prospective Outcomes Study will have 2 primary aims: to determine the feasibility of sufficient enrollment for a PONTT, and to measure clinically important outcomes in a prospectively studied cohort of children with PON.

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) in cooperation with the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC). It is funded through a cooperative agreement between the National Eye Institute and PEDIG, with the coordinating center at the Jaeb Center for Health Research, Inc (Tampa, FL). It will be a 4-year study, including 2 years of enrollment in a prospective data collection of children with acute optic neuritis in 1 or both eyes to assess our ability to enroll a sufficient number of patients for a future randomized controlled trial, and to evaluate systematically clinical outcomes in this population. Any investigator in North America caring for such patients who is a member of PEDIG or NORDIC, or is eligible and willing to join one of the groups, is encouraged to participate. Sites with NORDIC members who are not affiliated with PEDIG will be certified for this study as PEDIG affiliates. Each site will be required to have a principal investigator who is certified to lead the study and a research coordinator. Sites with an institutional review board (IRB) will be required to obtain local approval for the protocol and consent process. Sites without an IRB may participate after certification from the Jaeb Center IRB.

The Pediatric Optic Neuritis Prospective Outcome Study will include children who are 3 through 15 years with PON in at least 1 eye, and enrollment will occur over a 2-year period or until 100 subjects participate. For eligibility, onset of symptoms must be within 2 weeks of enrollment and patients will be required to undergo a MRI of the brain and orbits. Patients with neuroretinitis or a previous episode of ON in the recently affected eye(s) will be

excluded. Patients also will be excluded if they have meningitis or laboratory abnormalities consistent with CNS infection, malignancy, or other findings suggestive of a nondemyelinating cause for ON. Baseline testing will include high and low-contrast monocular visual acuity testing using the Electronic Visual Acuity System (17). Optional testing will include optical coherence tomography (OCT) and automated visual fields. Serum will be obtained for neuromyelitis optica IgG antibody (NMO-IgG), which will be analyzed at the Mayo Clinic (Rochester, MN) to provide standardization of the assay, and serum samples will be saved for future analyses. Treatment will be at investigator discretion.

The study's primary aim is to determine the network's ability to recruit for a randomized clinical trial. The primary outcome is high-contrast monocular visual acuity at 6 months after enrollment. Descriptive analyses and cross-tabulations of the distribution of monocular visual acuity will be stratified according to laterality of PON at presentation. The mean visual acuity deficit in the affected eye(s) 6 months after enrollment, estimated using normative data for age will be calculated by age group using a linear mixed model to adjust for the intereye correlation, as we will include both eyes of bilaterally affected children.

Secondary aims include characterization of ON in a large multicenter cohort of children, high-contrast, and low-contrast visual acuity measurements at 6 months, 1 year, and 2 years after enrollment, as well as the risk of developing MS at 2 years. In addition, the impact of NMO antibodies on clinical outcomes and quality of life measures will be analyzed. If OCT is performed, retinal nerve fiber layer and macular ganglion cell thickness will be measured and analyzed.

This Pediatric Optic Neuritis Prospective Outcomes Study represents an opportunity for neuro-ophthalmic and pediatric ophthalmic communities to work together to study a rare disease in children. If successful, this initial collaboration could be broadened to other pediatric neuroophthalmic disorders. We welcome participation from members or future members of NORDIC and PEDIG who express interest in participating in the study through email (pedig@jaeb.org).

REFERENCES

1. Liu GT, Volpe NJ, Galetta SL. Neuro-Ophthalmology: Diagnosis and Management. London, United Kingdom: Elsevier Saunders, 2010.
2. O'Mahony J, Marrie RA, Laporte A, Yeh EA, Bar-Or A, Phar C, Buckley D, Callen D, Connolly MB, Pohl D, Dilenge ME, Bernard G, Lortie A, Lowry N, MacDonald EA, Meek D, Sebire G, Venkateswaran S, Wood E, Yager J, Banwell B. Recovery from central nervous system acute demyelination in children. Pediatrics. 2015;136:e115–e123. [PubMed: 26034241]
3. Lana-Peixoto MA, Andrade GC. The clinical profile of childhood optic neuritis. Arq Neuropsiquiatr. 2001;59:311–317. [PubMed: 11460171]
4. Lucchinetti CF, Kiers L, O'Duffy A, Gomex MR, Cross S, Leavitt J, O'Brian P, Rodriguez M. Risk factors for developing multiple sclerosis after childhood optic neuritis. Neurology. 1997;49:1413–1418. [PubMed: 9371931]
5. Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C, Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. Neurology. 2006;67:258–262. [PubMed: 16864818]
6. Brady KM, Brar AS, Lee AG, Coats DK, Paysse EA, Steinkuller PG. Optic neuritis in children: clinical features and visual outcome. J AAPOS. 1999;3:98–103. [PubMed: 10221803]

7. Bonhomme GR, Waldman AT, Balcer LJ, Daniels AB, Tennekoon GI, Forman S, Galetta SL, Liu GT. Pediatric optic neuritis: brain MRI abnormalities and risk of multiple sclerosis. Neurology. 2009;72:881–885. [PubMed: 19273821]

8. Wan MJ, Adebona O, Benson LA, Gorman MP, Heidary G. Visual outcomes in pediatric optic neuritis. Am J Ophthalmol. 2014;158:503–507. [PubMed: 24907434]

9. Beck RW, Trobe JD, Moke PS; Optic Neuritis Study Group. High-and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. Arch Ophthalmol. 2003;121:944–9401. [PubMed: 12860795]

10. Waldman AT, Gorman MP, Rensel MR, Austin TE, Hertz DP, Kuntz NL. Pediatric central nervous system demyelinating disorders: consensus of United States neurologists. J Child Neurol. 2011;26:675–682. [PubMed: 21518802]

11. Trobe JD, Sieving PC, Guire KE, Fendrick AM. The impact of the optic neuritis treatment trial on the practices of ophthalmologists and neurologists. Ophthalmology. 1999;106:2047–2053. [PubMed: 10571336]

12. Optic Neuritis Study Group. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. Ophthalmology. 2008;115:1079–1082.e5. [PubMed: 17976727]

13. Filippini G, Brusaferri F, Sibley WA, Ciherio A, Ciucci G, Midgard R, Candelise L. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database Syst Rev. 2000:CD001331. [PubMed: 11034713]

14. Hickman SJ, Kapoor R, Jones SJ, Altmann DR, Plant GT, Miller DH. Corticosteroids do not prevent optic nerve atrophy following optic neuritis. J Neurol Neurosurg Psychiatry. 2003;74:1139–1141. [PubMed: 12876255]

15. Diem R, Hobom M, Maier K, Weissert R, Storch MK, Meyer R, Bahr M. Methylprednisolone increases neuronal apoptosis during autoimmune CNS inflammation by inhibition of an endogenous neuroprotective pathway. J Neurosci. 2003;23:6993–7000. [PubMed: 12904460]

16. Waldman AT, Shumski MJ, Jerrehian M, Liu GT. Parent and medical professional willingness to enroll children ina hypothetical pediatric optic neuritis treatment trial. Front Neurol. 2011;2:75, 1–4. [PubMed: 22164153]

17. Moke PS, Turpin AH, Beck RW, Ferris FL, Sangiovanni JP, Johnson CA, Birch EE, Chandler DL, Cox TA, Blair RC, Kraker RT. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. Am J Ophthalmol. 2001;132:903–909. [PubMed: 11730656]