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Clinical Features and Outcomes of Pediatric Monophasic and Recurrent Idiopathic Optic Neuritis

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Abstract

Limited data exist on isolated optic neuritis in children. We report the clinical features and treatment of pediatric subjects with monophasic and recurrent idiopathic optic neuritis. This retrospective cohort study of patients with isolated optic neuritis identified 10 monophasic and 7 recurrent optic neuritis cases. Monophasic optic neuritis patients were older (mean 13.3 ± 4.22) than those with recurrent idiopathic optic neuritis (9.86 ± 3.63). Females represented 50% of monophasic and 85.7% of recurrent idiopathic optic neuritis cases. Patients with monophasic optic neuritis were less likely to have a bilateral onset than recurrent idiopathic optic neuritis (40% vs 57.1%). Only 1 case had oligoclonal bands in the cerebrospinal fluid CSF. Most recurrent idiopathic optic neuritis cases had evidence of anti-myelin oligodendrocyte glycoprotein (MOG) antibodies (5/7). Treatment of recurrent idiopathic optic neuritis cases included intravenous pulse glucocorticosteroids and immunotherapy. We observed differences between recurrent and monophasic idiopathic optic neuritis. Immunosuppression appeared to prevent further relapses in recurrent idiopathic optic neuritis patients. Weaning immunotherapies after several years of quiescence in recurrent idiopathic optic neuritis may be possible, but larger studies are needed.

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Author Contributions

SJ and JG conceived the study, and SJ, JB, EW, and JG designed the study. SJ and JG drafted the manuscript. SJ, BY, HJ, PP, MR, KS, JB, EW, and JG acquired the data, and SJ, PP, MR, KS, JB, EW, and JG analyzed the data. All authors took part in interpretation of data and critically revised the manuscript and gave final approval.

Ethical Approval

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Keywords

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Optic neuritis refers to inflammation of the optic nerve that can be an isolated condition or related to different autoimmune disorders. The incidence of optic neuritis in children is 1–5 per 100 000 per year.¹ In a pediatric population, specific features include worse visual nadirs during acute optic neuritis, but better central acuity recovery and increased risk of bilateral involvement regardless of etiology.² Approximately 80% of children with optic neuritis will recover normal central acuity, but follow-up is often limited.³ Although several conditions, including multiple sclerosis, can present with optic neuritis, some cases appear to be idiopathic with negative brain and spinal cord imaging and unremarkable serologic and cerebrospinal evaluations.

The pathophysiology and natural history of idiopathic optic neuritis are not well understood. Idiopathic cases pose several management challenges, as there is a 30% to 50% likelihood of at least 1 recurrent episode in adult populations.⁴ Standard treatment for acute idiopathic optic neuritis is high-dose methylprednisolone, but if there is optic neuritis recurrence (defined as recurrence of acute symptoms >30 days from prior episode), immunosuppressants are often initiated to prevent relapses. There are concerns, however, regarding possible side effects associated with long-term use of such medications including secondary neoplasms.

As such, strong clinical need exists for a systematic description and definition of monophasic optic neuritis and recurrent idiopathic optic neuritis in the pediatric population in order to establish recommendations for management. In this retrospective study, we sought to describe demographic and clinical characteristics of patients with recurrent idiopathic optic neuritis and their outcomes in routine clinical practice to support future multicenter prospective studies.

Methods

Participants and Clinical Data

Participants presenting to UCSF Pediatric MS Center between July 2006 and June 2017 were considered for the study. Inclusion criteria were as follows: at least 1 episode of clinical optic neuritis; no evidence of an underlying autoimmune (such as multiple sclerosis or neuromyelitis optica as defined by recent published criteria⁵), infectious, or neoplastic disease; no magnetic resonance imaging (MRI) T2-bright abnormalities in the brain parenchyma or spinal cord; seronegative for aquaporin-4 antibodies. All patients seen in our clinic were tested for Lyme and Bartonella, if they had appropriate risk exposure, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), serum protein electrophoresis (SPEP), and rapid plasma reagin (RPR). All isolated optic neuritis cases were tested for anti-aquaporin-4 antibodies and have brain and spinal cord imaging performed. Additional tests are sent based on patient history and exposures. This cohort was recruited before availability of commercial anti-myelin oligodendrocyte glycoprotein

(MOG) testing. Clinical optic neuritis was defined as acute visual acuity impairment with color vision loss, pain, afferent pupillary defect (if unilateral), and central or other visual field defect. Other causes of visual loss were excluded.⁶ Demographic and clinic data were extracted from participants' medical records. Visual outcomes, laboratory values, and clinical and MRI reports were reviewed by the treating neurologists (EW, JG). Medication use, including start and stop dates of immunotherapies, was recorded.

Serologic Testing

Serum samples that had been collected at the participants' first visit as part of an ongoing registry study were later, when MOG testing was commercially available, sent to the University of Colorado School of Medicine and Medical University of Innsbruck (Reindl Laboratory) for screening of autoantibodies against MOG and novel autoantibodies. Serum samples were analyzed for binding to human MOG using a live cell-based assay as described by Peschl et al.⁷ MOG-IgG titers were determined by limiting dilution. For anti-MOG-negative samples, sera were applied to cryosections (12 µm) of human cerebellum. Optic nerve tissue was not available for testing. Sections were blocked with 5% goat serum in phosphate-buffered saline with 0.3% Triton X100 and 0.5 mg/mL of goat anti-human Fab (Jackson ImmunoResearch) for 1 hour, and then incubated with human sera (1/50 dilution) in 5% goat serum in phosphate-buffered saline with 0.3% Triton X100 overnight at 20°C. Slides were rinsed 3 times for 5 minutes with phosphate-buffered saline; then goat anti-human Alexa 594 Fc secondary antibody (1/500; Jackson ImmunoResearch) was added in 5% goat serum in phosphate-buffered saline with 0.3% Triton X100 for 2 hours. Slides were rinsed again 3 times for 5 minutes in phosphate-buffered saline and placed on coverslip using Prolong Gold plus DAPI as a mounting agent. Imaging was performed on an Olympus IX83 inverted microscope.

Regulatory Approval

The UCSF Human Research Protection Program IRB approved this study. Participants and their parents provided written assent and consent, respectively, to be included in a parent longitudinal cohort study of risk factors and phenotypes of pediatric demyelinating diseases.

Statistical Analysis

Given limited sample size, we performed qualitative analyses. Continuous variables were described by means and medians as appropriate and categorical variables by frequencies and percentages.

Results

We identified 17 eligible cases with an original diagnosis of idiopathic optic neuritis. Monophasic optic neuritis represented 10/17 cases. There were 7 cases of recurrent idiopathic optic neuritis with a median number of 2 (range: 2–4) events observed during a median of 3.77 years (range: 2.8–8.4) of follow-up. Some type of illness or trauma was present preceding the first optic neuritis in 1/10 monophasic optic neuritis cases and 4/7 recurrent idiopathic optic neuritis cases. At the time of the first event, only 1 case (monophasic) was receiving immune therapy for juvenile idiopathic arthritis (case 9), which

may have promoted optic neuritis. All non-Hispanic white individuals were found to have recurrence. Those individuals made up 67% of the recurrent cases. The average age of onset was older in the monophasic group compared to recurrent idiopathic optic neuritis (Table 1). In the recurrent idiopathic optic neuritis phenotype, there was a trend toward increased female to male ratio (85.7% vs 50%, $p = .13$). In monophasic, 40% of the first optic neuritis events were bilateral compared to 57.1% in recurrent idiopathic optic neuritis.

Mean time between first episode of optic neuritis and first brain/orbital MRI was 6.4 (SD = 5.17) days for monophasic cases and 1.4 (SD = 3.5) days for recurrent cases. On this MRI, 90% of monophasic participants had optic nerve enhancement, compared to 60% of recurrent idiopathic optic neuritis cases. No cases had orbital fat or optic nerve sheath enhancement. Eleven of the 17 cases had cerebrospinal fluid results available for review: only 1 patient with monophasic optic neuritis had oligoclonal bands.

Visual nadir information was limited because of initial evaluations outside our center. The central acuity nadirs of first events (available in 4 monophasic and 3 recurrent idiopathic optic neuritis cases) were typically worse in the monophasic group (Table 1). All monophasic optic neuritis events were treated with high-dose weight-appropriate steroids, compared to 57.1% of first events in recurrent idiopathic optic neuritis. Characteristics for each participant's first event are provided in Table 2. Recovery data for recurrent events is the most recently recorded acuity after last documented event. No participants received plasma exchange (PLEX).

Serum sample analysis results for monophasic and recurrent cases are shown in Table 2. In the monophasic group, 7/10 cases had samples tested: 3/7 had anti-MOG antibodies, and of the 4 patients who were anti-MOG negative, only 1 was positive for staining on cerebellar brain slices. Of note, the patient with juvenile idiopathic arthritis was negative for both antibodies. All recurrent idiopathic optic neuritis cases (7/7) had samples tested for autoantibodies, and all had evidence of CNS autoantibodies: 5/7 had anti-MOG antibodies, and both participants who were negative for anti-MOG had positive staining on human cerebellar brain slices. Regarding any potential differences in anti-MOG titers between groups, the titers were similar, ranging from 1:2560–10 240 in monophasic cases and from 1:1280–10 240 in recurrent.

Three (2/3 had anti-MOG antibodies) of the 7 recurrent idiopathic optic neuritis cases received chronic immunosuppressive therapy (in our cohort, mycophenolate mofetil) to prevent further episodes (Figure 1). None had another optic neuritis flare during the observed follow-up period (average = 6.67 years, SD = 2.51 years). One patient switched from mycophenolate mofetil to mycophenolic acid for better tolerability. Two cases have stopped immunosuppressive treatment, 2.3 and 2.6 years after initiation. No further optic neuritis events occurred in these cases for the ensuing 34 and 10 months, respectively, of follow-up off treatment.

Discussion

Previous studies in the literature have aimed to describe and define the entity of idiopathic optic neuritis in a pediatric population.^{3,4,8} Many of these publications consist of case reports and case series with limited numbers of subjects in any given study.^{3,4,8} The cases of optic neuritis in our study have several notable features. Most had excellent functional central acuity recovery after the first event and none required PLEX for acute therapy. Cerebrospinal fluid abnormalities were very uncommon, and in stark contrast to both multiple sclerosis and neuromyelitis optica, only 1 case had oligoclonal bands present in the cerebrospinal fluid, which further suggests that isolated optic neuritis is of a separate etiology than multiple sclerosis. Although our sample size was small, there was a trend toward fewer white non-Hispanic monophasic optic neuritis cases and female monophasic optic neuritis cases as compared to the recurrent idiopathic optic neuritis cases. Recurrent idiopathic optic neuritis cases on immune therapies remained event-free on treatment. Two of these individuals were able to stop medication without recurrence during follow-up. Larger and longer studies are needed, but our findings suggest that unlike multiple sclerosis, recurrent optic neuritis, including those cases with anti-MOG antibodies, may not require continuous, indefinite treatment.

Although at the time of diagnosis of our cases commercial MOG antibody testing was unavailable, retrospective testing was performed. In contrast to monophasic optic neuritis, all recurrent idiopathic optic neuritis cases either had anti-MOG antibodies or evidence of antibody staining against an unknown target in prepared cerebellar brain slices, indicating a different potential antigen target. For this additional staining, cerebellar brain slices were used as high-quality optic nerve tissue is challenging to obtain and maintain. When present in both groups, titers for anti-MOG antibodies were of similar range. With longer follow-up, it is possible that some of MOG-IgG positive monophasic optic neuritis patients will experience a recurrence of symptoms.⁹ Anti-MOG antibodies have been associated with phenotypes including encephalomyelitis, relapsing and bilateral optic neuritis, and transverse myelitis.¹⁰ MOG encephalomyelitis is a disease that causes inflammatory CNS demyelination that is similar in presentation to multiple sclerosis.¹¹ However, there are differences in immunopathogenicity that can have significant impacts on patient management.¹¹ MOG encephalomyelitis is a disease in which MOG-IgG has been shown to contribute to tissue injury.^{7,12,13} Although MOG-IgG contributes to tissue injury in animal models, its role in driving optic nerve and spinal cord inflammation in affected patients remains uncertain. Positive immunofluorescence staining of human cerebellar sections with MOG-seronegative sera provides tantalizing evidence that additional autoantigens may be contributory.

Previous literature shows that individuals with idiopathic optic neuritis often have a history of a preceding illness.¹ This appeared to be true among our recurrent idiopathic optic neuritis cohort as well. A number of participants had a preceding illness of assumed viral origin, but there were 2 unique cases in which seizure and a motorcycle accident preceded optic neuritis. The lack of a preceding event in most of the participants further emphasizes the current gap in understanding of the etiology of this condition and warrants further study. Additionally, previous literature has shown similar characteristics and outcomes among

individuals with idiopathic optic neuritis as were seen in our study.³ One unique case in our series was of a girl with juvenile idiopathic arthritis (JIA) who had a single monophasic event of optic neuritis. This type of event is very rare in JIA. A recent single case report in the literature¹⁴ reported a monophasic event of bilateral optic neuritis in a patient with JIA. To our knowledge, neither our case nor this reported case was exposed to a tumor necrosis factor alpha inhibitor medication (these medications have been reported to trigger demyelinating events).

Our study is consistent with prior case reports and contributes new valuable information.^{3,4,8} The lack of oligoclonal bands (OCBs) and response to steroids without need for PLEX in these patients are valuable features relevant to clinical practice that have not previously been reported for this population. The lower rates of treatment with steroids among the recurrent idiopathic optic neuritis group could be attributed to the fact that the cases were less severe on presentation. Conversely, it may be possible to argue that lack of treatment with high-dose steroids could have contributed to the development of recurrence. The presence of autoantibodies to MOG in some of the studied patients suggests that this testing should be considered in pediatric optic neuritis patients with first-time acute events and always in recurrent cases.

The limitations of this study include the modest sample size and retrospective design, though given the rarity of the disease, this is a comparatively large collection of isolated optic neuritis cases in children from a single center. The relatively short follow-up is a limitation for the monophasic cases as they may still be at risk for recurring optic neuritis events in the future. Although our sample size precludes definitive treatment recommendations, it is encouraging that immune therapy in recurrent idiopathic optic neuritis patients was associated with lack of optic neuritis recurrence.

Future studies are needed to better understand this clinical entity. Given the low frequency with which these cases are observed, multicenter trials are needed. Prospective studies will allow for systematic capture of visual data in acute and follow-up periods. Either observational or interventional studies would be appropriate and contribute to the knowledge of this disease. This will ultimately lead to not only improvement in management of these cases but also to improved management parameters to avoid unnecessary treatment with immune therapies.

This study provides a valuable and substantial addition to the scarce literature regarding the entity of pediatric isolated optic neuritis. Although decisions regarding patient management based on this article alone would be inappropriate, it can be used as a source to contribute to the management and spectrum of disease for patients with this nuanced and challenging condition.

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Declaration of Conflicting Interests

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Figure 1.

Timeline of recurrent idiopathic optic neuritis cases. Bars represent the duration of follow-up with each event designated by a triangle for time of onset. All immunosuppressed participants were treated using mycophenolate. Cases 11 and 17 have magnification to emphasize separation of individual events.

Summary of First Events.

Table 1.

	Monophasic ON (n = 10)	Recurrent ON (n = 7)
Mean age of onset $\pm$ SD	13.3 $\pm$ 4.22	9.86 $\pm$ 3.63
Female, n (%)	5/10 (50)	6/7 (85.7)
Bilateral first events, n (%)	4/10 (40)	4/7 (57.1)
Nonwhite, n (%)	10/10 (100)	2/6 (33.3) ^a
Acute optic nerve enhancement MRI, n (%)	9/10 (90)	3/5 (60)
OCB present, n (%)	1/8 (12.5)	0/3 (0)
Elevated IgG index >0.6, n (%)	1/8 (12.5)	0/3 (0)
CSF white blood cells >4, n (%)	3/8 (37.5)	1/4 (25)
Median first 25-OH vitamin D, ng/mL (range)	17 (12–34)	24 (9–29)
Median months' duration of follow-up (range)	11.63 (2.87–62.09)	55.32 (33.98–100.26)
Median decimal central acuity nadir (range)	0.075 (0.05–0.29) (n = 4) ^b	0.1 (FC-0.5) (n = 3) ^{b,c}
Mean decimal central acuity nadir	0.12 (n = 4)	0.21 (FC-0.5) ^c (n = 3)
Median central acuity recovery ^d	1 (n = 7)	1 (n = 2)
First event treated with steroids, n (%)	10/10 (100)	4/7 (57.1)
Median sedimentation rate (range) ^e	26 (10–43) (n = 8)	15 (7–34) (n = 6)
Median no. of events/subject (range)	1	2 (2–4)

Abbreviations: CSF, cerebrospinal fluid; FC, finger counting; MRI, magnetic resonance imaging; OCB, oligoclonal bands; ON, optic neuritis; SD, standard deviation.

^aOne participant was documented as declined/unknown.

^bLimited availability as many were referred in from outside sources with no formal acuity at event is documented or have another event before central acuity recovery was measured.

^cAcuity of 20/800 (0.025) used as equivalent for finger counting.

^dRepresents final visual acuity after recovery. Recovery considered to be greater than 3 months after event and/or return to baseline vision.

^eFirst available sedimentation rate at/after onset.

Table 2.

Seventeen Cases of Pediatric Optic Neuritis (First Event).

Case no.	Sex	Age of onset	No. of events	Unilateral or bilateral	Eye pain present	Preceding illness/trauma	Acute central acuity nadir (decimal)	Recovery central acuity (decimal)	Acute optic nerve enhancement	CSF WBC >4	IgG index	OCB	25-OH vitamin D level ^a	Anti-MOG Ab status	Immunofluorescence
Monophasic															
1	F	16	1	U	+	–	20/200 (0.1)	n/a	+	–	0.83	–	n/a	n/a	n/a
2	F	5	1	B	–	–	n/a	20/20 (1)	+	–	–	–	n/a	n/a	n/a
3	M	11	1	S	+	+	n/a	20/20 (1)	+	8	0.53	–	26.3	+	n/p
4	F	17	1	U	+	–	20/70 (0.29)	n/a	+	n/a	n/a	n/a	34	–	–
5	F	16	1	B	+	–	n/a	20/20 (1)	+	–	–	–	12	–	+ GCL
6	M	18	1	U	+	–	n/a	20/40 (0.5)	+	5	0.42	5	13	–	–
7	M	15	1	B	+	–	20/400 (0.05)	20/25 (0.8)	+	6	0.5	–	20	+	n/p
8	M	8	1	B	+	+	n/a	20/20 (1)	+	–	0.53	–	16	+	n/p
9	F	15	1	U	+	–	n/a	20/20 (1)	+	n/a	n/a	n/a	17	–	–
10	M	12	1	S	–	–	20/400 (0.05)	20/50 (0.4)	–	–	0.5	–	n/a	n/a	n/a
Recurrent															
11	F	8	4	B	–	–	n/a	n/a	–	–	–	–	24	+	n/p
12	F	10	2	B	–	–	20/200 (0.1)	20/20 (1)	+	n/a	–	–	15	+	n/p
13	F	8	2	B	–	+	n/a	n/a	n/a	17	n/a	n/a	27	+	n/p
14	F	9	4	U	+	+	n/a	20/20 (1)	–	–	0.37	–	29	–	+ GCL
15	F	13	2	B	+	–	FC	n/a	+	n/a	n/a	n/a	9	+	n/p
16	F	16	2	U	+	^b	n/a	n/a	n/a	n/a	n/a	n/a	n/a	–	+ GCL
17	M	5	4	U	–	+	20/40 (0.5)	n/a	+	–	n/a	n/a	n/a	+	n/p

Abbreviations: Ab, antibody; B, bilateral; CSF, cerebrospinal fluid; F, female; FC, finger counting; +GCL, staining of granule cell layer in human cerebellum; M, male; n/a, indicates sample not available for testing; No., number; n/p, indicates not performed due to positive anti-myelin oligodendrocyte glycoprotein (MOG) result; OCB, oligoclonal band; S, sequential; U, unilateral; Vit., vitamin.

^aFirst available 25-OH vitamin D.

b_{Trauma}

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