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Clinical Characteristics and Visual Outcomes of Pediatric Optic Neuritis: A Single Center Experience

Pediatrik Optik Nörit Hastalarının Klinik Özellikleri ve Göz Bulguları: Tek Merkez Deneyimi

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Abstract

Introduction: The aim of this study was to describe the clinical characteristics, visual outcomes of pediatric patients presenting with first-episode of optic neuritis.

Materials and Methods: We reviewed medical records of the patients newly diagnosed with optic neuritis younger than 18 years between January 2014 and December 2018 retrospectively.

Results: Twenty-eight patients were included to this study. The mean age at first onset of optic neuritis was 13.2±3.1 (range 6.2-17.3) years. The mean follow-up period was 4.2±3.2 (range 0.6-13.08) years. Seven (25%) patients had recurrent optic neuritis. Optic neuritis involvement was unilateral in 17 (60%) patients. Forty percent of the patients had idiopathic optic neuritis. Of the six patients with demyelinating lesions in cranial magnetic resonance imaging (MRI) at the first admission, three were diagnosed with multiple sclerosis (MS) at the time of first optic neuritis attack, and three were diagnosed within 13.4±4.8 months after the first episode. Eight (38%) of 21 optic neuritis patients had oligoclonal band positivity and the incidence of MS was significantly higher in these patients (p=0.014). The mean visual acuity at nadir was 0.48±0.27 at admission. Whereas it was 0.74±0.31 and 0.76±0.33 at 1 and 6 months respectively. There was a strong correlation between first and sixth-month visual acuity (r=0.98, p=0.001).

Conclusion: Our study demonstrated that poor visual acuity (worse than 0.5) at 1 month can predict poor vision at 6 months. The patients with demyelinating lesions in cranial MRI at their first optic neuritis episode, are more likely to develop MS during the follow-up.

Keywords: Optic neuritis; children; visual acuity; multiple sclerosis.

Özet

Amaç: Bu çalışmanın amacı, ilk kez optik nörit atağı ile başvuran çocuk hastaların klinik özelliklerini ve göz bulgularını tanımlamaktır.

Gereç ve Yöntem: Ocak 2014 ile Aralık 2018 tarihleri arasında 18 yaşından küçük, optik nörit tanısı alan hastaların tıbbi kayıtları geriye dönük olarak tarandı.

Bulgular: Bu çalışmaya 28 hasta dahil edildi. Optik nöritin ilk başlangıç yaşı ortalama 13,2±3,1 (6,2-17,3) yıl idi. Ortalama takip süresi 4,2±3,2 (0,6-13,08) yıldı. Hastaların 7 (%25)'sinde tekrarlayan optik nörit vardı. Optik nörit tutulumu 17 (%60) hastada tek taraflıydı. Hastaların %40'ında optik nörit idiyopatikti. İlk başvuruda beyin manyetik rezonans görüntülemede (MRG) demiyelinizan lezyonu olan altı hastanın üçüne ilk optik nörit atağı sırasında multipl skleroz (MS) tanısı kondu. Üçüne ise ilk optik nörit atağından sonra ortalama 13.4±4,8 ay içinde MS tanısı konuldu. Yirmi bir optik nörit hastasının sekizinde (%38) oligoklonal bant pozitifliği vardı ve bu hastalarda MS insidansı anlamlı olarak daha yüksekti (p=0.014). Hastaların ilk başvuru anında en düşük ortalama görme keskinliği Snellen testine göre 0.48±0.27 idi. Birinci ve 6. ayda sırasıyla Snellen testine göre 0.74±0.31 ve 0.76±0.33 idi ve birinci ve 6. ay görme keskinliği arasında güçlü bir ilişki vardı (r=0.98, p=0.001).

Sonuç: Çalışmamızda, optik nörit tanısı alan hastaların 1. aydaki görme keskinliğinin düşük olmasının (0,5'ten daha kötü) 6. ayda görme keskinliğinin kötü olabileceğini öngörebildiği gösterilmiştir. İlk optik nörit atağında beyin MRG'de demiyelinizan lezyonların olması, takiplerde MS gelişebilmesi açısından risk faktörü olabilir.

Anahtar Kelimeler: Optik nörit; çocuk; görme keskinliği; multiple skleroz.

Introduction

Optic neuritis (ON) can be defined as a visual dysfunction due to the pathologic inflammatory process of one or both optic nerves. Decreased visual acuity (VA), visual field (VF) deficits, dyschromatopsia (abnormal color vision, notably red color desaturation) are the cardinal features of optic neuritis (1). The incidence of ON is 1-5 per 100,000 per year (2-4). Although it is often seen in

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isolated idiopathic form in children, ON may be a part of other central nervous system demyelinating diseases such as acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS) and neuromyelitis optica (NMO) (5,6). The risk of developing MS is low in children with bilateral optic neuritis (7). Recurrent optic neuritis is more associated with autoimmune or demyelinating diseases such as MS or NMO (8). Pediatric optic neuritis is typically associated with visual recovery, but some patients may have significant visual loss (9, 10). It is important to determine the predictive factors of a poor visual outcome for predicting the prognosis. The aim of this study was to describe the clinical characteristics, visual outcomes and final diagnosis of pediatric patients presenting with first-episode of optic neuritis.

Materials and Methods

This is a retrospective study performed at the Department of Pediatric Neurology, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital. We reviewed medical records of the patients newly diagnosed with optic neuritis younger than 18 years between January 2014 and December 2018. The demographic data, initial ophthalmological symptoms, detailed history for other neurological and systemic symptoms, recent infections or vaccination, family history of autoimmune disorders were collected from their medical files. Optic neuritis defined as an acute loss of vision at presentation, with one or more of the following: visual field deficit, relative afferent pupillary defect (RAPD), impaired color vision, optic disc edema/swelling or abnormal visual evoked potentials (VEP). Patients with an uncertain diagnosis, unavailable clinic data or inadequate follow-up were excluded. Optic neuritis was interpreted if it is an isolated ON or as a part of other demyelinating diseases. We also recorded if there is a progression to other demyelinating diseases. The patients with demyelinating etiology, recent infections or vaccination and autoimmune disorders were classified as symptomatic. Also, optic neuritis following a febrile infection in 7-14 days and patients having a history of vaccination in 3 months were also categorized in symptomatic group. Recurrent ON was defined as a new episode occurred at least four weeks after the initial event (11). The patients had an ophthalmologic evaluation by an ophthalmologist. Details of the ophthalmological examination including visual acuity at nadir, presence or absence of RAPD, visual field assessment, color vision test and VEP results were noted. At funduscopic examination; optic disc findings were classified into two groups; normal (retrobulbar neuritis) and optic disc edema/swelling (papillitis). Optic neuritis was also categorized as bilateral or unilateral according to the eye involvement. Visual acuity was evaluated with Snellen chart and scored between 0 and 1. Ophthalmoscopic evaluations were performed in all patients at the admission and repeated at first and sixth months in patients who keep up their ophthalmoscopic follow-up. It was also repeated if ON is relapsed. The control examinations were categorized as full recovery, partial recovery and optic atrophy and also as visual acuity better or worse than 0.5. All patients underwent routine blood tests including total blood cell count, serum electrolytes and glucose concentrations, renal and hepatic functions, serology for infections, markers for vasculitis syndromes such as rheumatoid factor (RF), antinuclear antibodies (ANA), antiphospholipid and anticardiolipin antibodies, anti-Sjogren's-syndrome-related antigen A (SSA), anti-Sjogren's-syndrome-related antigen B (SSB) antibodies. The biochemical and microbiological findings of cerebrospinal fluid (CSF) and presence of oligoclonal band (OCB) in children who underwent lumbar puncture were recorded. Magnetic resonance imaging (MRI) of brain and orbital were performed in all patients. Spinal MRI was performed when necessary. Evaluation of the patients with optic neuritis in our pediatric neurology clinic was not standardized because patients were evaluated by different pediatric neurologists. However, all patients with ON at acute stage were treated with intravenous (iv) methylprednisolone (20-30 mg/kg/day, max 1 g/day) for 3–5 days. Pulse methylprednisolone treatment generally followed by an oral prednisolone (starting dose 1-2 mg/kg/day, max 60 mg/day) and tapered with varying durations in most of the patients. Patients were followed up for at least 6 months.

Ethical Consent: The study was performed according to the Helsinki Guidelines and approved by institutional review board of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (Approval number: 2019-176).

Statistical Analyses: Statistical analyses were performed using the SPSS software version 22 software package. Descriptive data are summarized as mean and standard deviation. Kruskal-Wallis tests were used to determine differences between the study groups. While investigating the associations between non-

normally disturbed and/or ordinal variables, the correlation coefficients and their significance were calculated using Spearman test. A linear regression model was used to identify independent predictors of visual acuity at nadir. A 5% type-1 error level was used to infer statistical significance. P values

Table 1: Demographics and clinical characteristics of patients with optic neuritis

	N (%)
Number of patients	28 (100%)
Age at first onset (years)	
Mean/Median (Range)	13.2±3.1/ 14.1 (6.2-17.3)
Age groups at first onset	
<10 years/ ≥10 years	7 (25%)/ 21 (75%)
Gender	
Female/ Male	19 (68%)/ 9 (32%)
Follow up period (years)	
Mean/Median (Range)	4.2±3.2/ 3.05 (0.6-13.08)
Underlying etiology	
Isolated idiopathic optic neuritis	11 (%40)
Demyelinating disease	7 (%25)
Vaccination (in the last 3 months)	4 (%14)
Recent infection (within the last 7-14 days)	4 (%14)
Vasculitis (Familial Mediterranean Fever and Sjogren disease)	2 (%7)
CSF analysis	25/28 (90%)
Increased protein level	5/25 (20%)
Oligoclonal band positivity	8/21 (38%)
High levels of Ig G index	7/21 (33%)
AQP4 antibody positivity	1/5
MRI findings	
Normal	13 (46%)
Enhancement of optic nerve	7 (25%)
Intracranial demyelinating lesions	6 (21%)
Spinal demyelinating lesions	2/7 (28%)
Treatment at acute attack	
Iv methylprednisolone only	4 (14%)
Iv methylprednisolone + oral steroids	23 (82%)
Iv methylprednisolone + oral steroids + iv immunoglobulin	1 (4%)
Number of attacks	
One attack/ Recurrent attacks	21/28 (%75)/ 7/28 (%25)
Time interval between first and second attack	
Mean/ Median (Range)	12.3±5.1/ 11.3 (6.5-19.06)

of <0.05 were considered significant. The study was performed according to the Helsinki Guidelines and approved by local ethics committee (Approval number: 2019-176).

Results

Demographics and Clinical Characteristics: Twenty-eight patients were included to this study with a female gender dominance (68%). The mean age at first onset of optic neuritis was 13.2±3.1 (range 6.2-17.3) years. Mean follow-up period was 4.2±3.2 (range 0.6-13.08) years. The clinical and demographic characteristics of the patients are summarized in Table 1. Seven of 28 (25%) patients had recurrent optic neuritis. Gender, age at diagnosis, unilateral or bilateral involvement, funduscopic findings or progression to MS were not different between recurrent or isolated ON groups.

Etiology: Forty percent of the patients had idiopathic optic neuritis as no underlying etiology was demonstrated. Demyelinating diseases were detected in 25% of patients (Table 1). The mean age at diagnosis between the idiopathic and symptomatic groups was not statistically different. A history of tetanus vaccination was recorded in four female patients. Three of these patients had retrobulbar neuritis and involvement was unilateral in two of them. Four patients had a history of recent infection. Three of four patients had unilateral retrobulbar optic neuritis. Six of 8 (75%) patients with a history of vaccination or infection had single optic neuritis attack. One of the patients was presented with recurrent optic

neuritis and diagnosed as Familial Mediterranean Fever (FMF) in follow-up. Another patient who only admitted with optic neuritis and no other disease specific symptoms was diagnosed as

Table 2: Etiologies and OCB features according to optic neuritis involvement and number of attacks

Laterality	
Unilateral	17 (60%)
Bilateral	11 (40%)
Fundoscopy findings	
Normal (Retrobulbar neuritis)	16 (57%)
Edema/Swelling (Papillitis)	12 (43%)
Relative afferent pupil defect	
Present	24 (85%)
Color vision	
Abnormal	20 (71%)
VEP*	18 (60%)
Abnormal	16/18 (88%)

***p=** 0.008 between recurrent optic neuritis and OCB positivity.

Table 3: Ophthalmological findings of patients with optic neuritis at first admission

	Optic neuritis involvement		Number of attacks	
	Bilateral (n: 11)	Unilateral (n: 17)	İsolated (n: 21)	Recurrent (n: 7)
Etiology				
Demyelinating	2	5	3	4
Vasculitis	0	2	1	1
Infection/	2	5	6	1
Vaccination	7	5	11	1
Idiopathic				
OCB				
Negative	5	8	10	3
Positive	3	5	5	3*

*Visual evoked potential

Table 4: Visual acuity at nadir in follow-up ophthalmological examination

	At admission	1 month	6 months
Mean ± standard deviation (SD)	0.48 ± 0.27	0.74 ± 0.31	0.76 ± 0.33
Median, interquartile range (IQR)	0.50 (0.50)	0.80 (0.40)	1.00 (0.40)

p=*0.001 between VA at admission and 1 month*
p=*0.001 between VA at admission and 6 months*

Sjogren disease according to anti-SSA and anti-SSB seropositivity and histopathologic findings of salivary gland biopsy. Gender, age, funduscopic findings at diagnosis, number of attacks, OCB and follow-up ophthalmoscopic examinations were not associated with underlying etiology.

Laboratory Findings: Cerebrospinal fluid findings were available for 25 children (Table 1). The biochemical and microbiological findings of CSF were normal in 80% of patients. OCB was measured in 21 of 28 patients. Eight (38%) of 21 patients had oligoclonal band positivity. OCB positivity was significantly high in patients with

recurrent optic neuritis (p= 0.008) (Table 2). Three of the oligoclonal band positive patients were diagnosed with MS at the first admission. And also, MS developed in the follow-up of two other oligoclonal band positive patients. Only one of the 13 OCB negative patients developed MS. The incidence of MS was significantly higher in patients who were positive for OCB (p=0.014).

Aquaporin 4 (AQP 4) antibodies were studied in five patients. Three of these five patients had one attack and two had recurrent attacks. Four of these patients had cranial or spinal demyelinating lesions and anti- AQP4 antibodies were negative. There was a single patient with positive AQP4 antibody. Sixteen-year-old male patient with recurrent optic neuritis had vision loss and numbness of left arm and leg at his seventh admission. The cervical MRI revealed diffuse signal intensities at the brain stem extending to the thoracic 7 vertebrae. This patient with positive AQP4 antibody was diagnosed as NMO. Myelin oligodendrocyte glycoprotein (MOG) antibody was not studied in our patients due to the unavailability in the first years of this study and inability of families to afford it in recent years.

MRI Manifestation: All 28 patients had brain and orbital MRIs and they were normal in 46% of the patients. Six patients had cranial demyelinating lesions at the first admission. Three of them diagnosed with MS as the demyelinating lesions met the criteria for pediatric MS (12). Three patients with demyelinating lesions developed MS 13.4±4.8 months after the first optic neuritis episode. Spinal MRI performed in seven patients. Two of them have spinal demyelinating lesions in spinal cord. One of these patients was the child that diagnosed with NMO, and the other one was that diagnosed with MS during the follow-up.

Ophthalmologic Examinations: Ophthalmological features are reported in Table 3. All patients had symptoms of visual loss. Sixteen (57,1%) patients had retrobulbar neuritis with normal fundoscopic findings whereas papillitis was demonstrated in 12 (42,9%) patients. Optic neuritis involvement was unilateral in 17 of 28 (60,7%) patients. Number of attacks, underlying etiology and age at diagnosis did not differ between unilateral and bilateral ON groups. VEP applicated in 18 of 28 patients. It was prolonged bilaterally in 5 patients and unilaterally in 1 patient.

Treatment: All the patients were treated with iv methylprednisolone (20-30 mg/kg/day, max 1 g/day) for 3–5 days and then 82% of patients underwent oral prednisolone treatment with a dose of 1-2 mg/kg/day, max 60 mg/day) In only one patient, iv immunoglobulin was added to the treatment as the attack could not be controlled with iv and oral steroids.

Visual Outcomes and Clinical Prognosis: The mean visual acuity at nadir was 0.48± 0.27 at admission. Whereas it was 0.74 ± 0.31 and 0.76 ± 0.33 at 1 and 6 months respectively (Table 4). Visual acuity after treatment was statistically higher than before treatment (p=0.00). There was a strong correlation between first and sixth-month visual acuity (r=0.98, p=0.00). However, first- and sixth-month visual acuity did not differ between treatment groups. Visual acuity at 6 months was better in patients younger than 10 years of age than those older than 10 years (p=0.0.12). Gender, funduscopic examination, number of attacks, underlying etiology, OCB positivity or unilateral/bilateral involvement were not correlated with visual acuity at sixth months. Twenty-three of 28 patients had last ophthalmoscopic follow-up at sixth month. Visual acuity was better than 0.5 in 20 (87%) of 23 children at sixth month. Visual acuity at sixth month was better than 0.5 in 15 of 16 (93%) isolated ON and 5 of 7 (72%) recurrent ON group. However, the difference between the groups was not statistically significant. Ten (43%) patients fully recovered where 11 (48%) patients had partial recovery. Progressive visual loss and optic atrophy developed in three (13%) patients. These were the patients who diagnosed with NMO, Sjogren disease and FMF. Three of six patients who diagnosed with MS fully recovered. Overall, all MS patients had visual acuity better than 0.5 at their last follow-up. Age at diagnosis, gender, fundoscopic findings, unilateral or bilateral involvement, visual acuity at admission, MS progression or underlying etiology were not associated with good visual outcomes. Visual acuity fully recovered in 6 of 11 (54%) patients in bilateral ON group and 4 in 17 (28%) patients in unilateral ON group. The difference between unilateral and bilateral ON groups was statistically significant (p=0.033). All 3 patients with optic atrophy had unilateral involvement.

Discussion

In this study we report the visual outcomes and clinical characteristics of pediatric patients with optic neuritis. Infectious-related ON and isolated ON found more frequently in children younger than 10 years, whereas children older than 10 years more frequently had MS after first ON (13). Although all the patients with demyelinating etiology were older than 8 years, age at diagnosis did not differ between the idiopathic and

symptomatic groups in our study. ON presents as retrobulbar neuritis in two thirds of adult patients whereas papillitis is more common in children (14). In our study funduscopic findings were compatible with retrobulbar neuritis in 58% of patients. Furthermore, it is reported that children are more likely to have bilateral involvement (15, 16, 17). In contrast, unilateral involvement was higher in our study. The similar rates of retrobulbar neuritis and unilateral involvement to adults seen in our study may be due to the fact that 75% of our patients were older than 10 years. Optic neuritis has also a good response to steroid treatments (18). Various studies have reported that improvement in visual acuity is better in children (15, 16, 17). Similar to previous studies 23 of 25 patients (87%) who evaluated at 6 months have visual acuity better than 0.5 in our study. Besides 32% of our patients were fully recovered. Full recovery rates were significantly higher in children with bilateral involvement. Sun et al. reported that patients who were 10 years of age or younger achieved final VA of 20/40 or better (17). Likewise, there was a statistically significant better visual outcome in children younger than 10 years old in our study. Similar with a retrospective study; visual acuity at presentation, bilateral involvement, sex, optic disc edema, and underlying diagnoses were not associated with poor visual outcomes in our patients (19). The presenting symptom is optic neuritis in 25% of multiple sclerosis patients (20,21). It is reported that 13-50% of children with a first episode of optic neuritis are diagnosed with MS in follow-up (13, 22, 23). ON being the first manifestation of MS is high in children with white matter lesions on brain MRI (13, 21). In our study three of six patients with cranial demyelinating lesions diagnosed with MS at their first ON episode. Other three patients with demyelinating lesions developed MS 13.4±4.8 months after the first optic neuritis episode. Frequency of MS was 21% (6/28 patients) in our study. CSF markers may help to determine risk for MS in children with an isolated-ON event. CSF oligoclonal bands were found in 80% of pediatric patients with MS and in only 15% of children with monophasic ON (23). Similar to previous studies the incidence of MS was significantly higher (62.5%) in patients who were positive for OCB in our study. In our study, Aquaporin 4 (AQP 4) antibodies were studied in five patients. There was a single patient with positive AQP4 antibody that also reported earlier in the literature (24). Optic Neuritis Study Group reported that visual improvement is slightly correlated with initial degree of visual loss (13, 22). However, we did not find any correlation between visual improvement and initial visual acuity. In our study the visual acuity at 1 month was strongly correlated with visual acuity at 6 months. This was similar with the study reported by Kupersmith at el. that, a cut-off level of vision ≤ 20/50 (6/15) after 1 month was predictive of a poor visual outcome at 6 months (25).

Study Limitations: The first limitation of our study was that no MOG antibody was studied in any of our patients. In addition, NMO antibody was studied in limited number of patients. Another important limitation of our study was that the study was retrospective in nature. It would be ideal to conduct prospective clinical trials on visual outcomes of pediatric optic neuritis.

Conclusions: In conclusion, the long-term visual prognosis of idiopathic optic neuritis remains good. More than 90% of the patients recover a visual acuity of 20/40 or better by 6 months (15). Our study demonstrated that pediatric optic neuritis has a good prognosis with visual acuity better than 0.5 in 87% of children. Poor acuity (worse than 0.5) at 1 month can predict poor vision at 6 months. The patients with demyelinating lesions on cranial MRI at their first optic neuritis episode, are more likely to develop MS during the follow-up.

Ethics Committee Approval: This study was approved by institutional review board of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (Approval number: 2019-176).

Conflict of Interest: The authors declare no conflict of interest to disclose for this study.

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