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Treatment Outcomes with the Optic Neuritis Treatment Trial Protocol in Typical Optic Neuritis and Prognostic Factors Associated with Final Visual Acuity: Real-Life Data

Tipik Optik Nöritte Optik Nörit Tedavi Denemesi Protokolü ile Tedavi Sonuçları ve Sonuç Görme Keskinliği ile İlişkili Prognostik Faktörler: Gerçek Yaşam Verileri

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ABSTRACT

Aim: This study aims to evaluate the etiological, demographic, and clinical characteristics of patients diagnosed with typical optic neuritis and treated according to the optic neuritis treatment trial (ONTT) protocol, as well as to assess prognostic factors associated with long-term visual acuity.

Materials and Methods: A retrospective analysis was conducted on 106 patients treated with the ONTT protocol at a tertiary eye clinic between January 2010 and June 2023. The patients' age, gender, affected eye, initial and final best-corrected visual acuity (BCVA), anterior or retrobulbar form of optic neuritis, presence of relative afferent pupillary defect, and visual field defects were evaluated. Factors influencing long-term visual acuity after treatment were analyzed.

Results: Of the patients, 57.5% were female, with a mean age of 32.25±12.79 years. Optic neuritis was observed in 53.7% of right eyes and 46.3% of left eyes. Multiple sclerosis (MS) was diagnosed in 13.2% of patients. The mean initial BCVA was 0.33±0.41, while the final BCVA was 0.65±0.38. A higher initial BCVA (p=0.01) and the presence of retrobulbar optic neuritis (p=0.04) were significantly associated with better long-term visual prognosis.

Conclusion: Most patients with typical optic neuritis treated with the ONTT protocol experienced improved visual acuity. Higher initial BCVA and retrobulbar optic neuritis were identified as positive prognostic factors. Long-term follow-up of patients with potential MS and larger-scale studies are necessary.

Keywords: Anterior, neuritis, optic, prognosis, retrobulbar, visual acuity

ÖZ

Amaç: Bu çalışma, tipik optik nörit tanısı konulan ve optik nörit tedavi denemesi (ONTT) protokolüne göre tedavi edilen hastaların etiyolojik, demografik ve klinik özelliklerini inceleyerek, uzun dönem görme keskinliği ile ilişkili prognostik faktörleri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Üçüncü basamak bir göz kliniğinde Ocak 2010 - Haziran 2023 tarihleri arasında ONTT protokolü ile tedavi edilen 106 hasta retrospektif olarak incelendi. Hastaların yaş, cinsiyet, etkilenen göz, başlangıç ve sonuç en iyi düzeltilmiş görme keskinliği (EİDGK), optik nöritin anterior veya retrobulber formda olması, rölatif afferent pupil defekti varlığı ve görme alanı defektleri değerlendirildi. Tedavi sonrası uzun dönem görme keskinliği ile ilişkili faktörler analiz edildi.

Bulgular: Hastaların %57,5'i kadın olup yaş ortalaması 32,25±12,79 olarak hesaplandı. Optik nörit, hastaların %53,7'sinde sağ gözde, %46,3'ünde sol gözde görüldü. Hastaların %13,2'sinde multipl skleroz (MS) tanısı mevcuttu. Başlangıç EİDGK ortalaması 0,33±0,41, sonuç EİDGK ortalaması ise

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0,65±0,38 idi. Başlangıç EİDGK'nin yüksek olması (p=0,01) ve retrobulber optik nörit varlığı (p=0,04), uzun dönem görme prognozunun daha iyi olmasıyla anlamlı ilişki gösterdi.

Sonuç: ONTT protokolü ile tedavi edilen tipik optik nörit hastalarının büyük çoğunluğunda görme keskinliği olumlu etkilenmektedir. Başlangıç EİDGK ve optik nöritin retrobulber formda olması, olumlu prognostik faktörler olarak belirlenmiştir. MS ile ilişkili olabilecek hastaların uzun vadeli takibi ve daha geniş ölçekli çalışmalar gerekmektedir.

Anahtar Kelimeler: Anterior, nörit, optik, prognoz, retrobulber, görme keskinliği

INTRODUCTION

Optic neuritis is characterized by inflammation of the optic nerve, causing acute, unilateral, painful vision loss[1]. Only 0.4% of patients develop symptoms in both eyes simultaneously[2]. The presumed pathophysiology of optic neuritis is inflammation and demyelination of the optic nerve. Activated peripheral T-cells cross the blood-brain barrier and release cytokines and other inflammatory mediators, leading to neuronal cell death and axonal degeneration[3]. It occurs most commonly in young adults and more frequently in women[4]. The incidence of optic neuritis is greater at higher latitudes compared with geographic locations closer to the equator[5]. The worldwide incidence of unilateral optic neuritis ranges from 0.94 to 2.18 per 100,000 per year[6].

There is no consensus on a systematic classification of optic neuritis. Studies often use different classification systems. Optic neuritis is traditionally divided into typical and atypical forms on clinical grounds. Typical optic neuritis is considered to be a clinically isolated demyelinating syndrome that presents as idiopathic optic neuritis and is at risk of developing into multiple sclerosis (MS) in the white population, or is associated with MS[7]. Thus, most cases of optic neuritis are due to idiopathic inflammatory demyelination, which can occur in isolation or as a manifestation of MS[8]. In atypical optic neuritis, recovery of visual acuity may be poorer and the risk of developing optic nerve atrophy may be greater in patients with idiopathic or MS-related optic neuritis than in patients with typical optic neuritis[9]. Atypical cases are characterized by the absence of eye pain, the presence of exudates and hemorrhages on examination, very severe, bilateral, or progressive visual loss, or failure to regain vision. These atypical optic neuritis cases include neuromyelitis optica, autoimmune optic neuropathy, chronic recurrent inflammatory optic neuropathy, idiopathic recurrent neuroretinitis and optic neuropathy associated with systemic diseases[10]. Typical optic neuritis is the initial symptom of MS in 25% of cases, and long-term follow-up studies have reported conversion to clinically definite MS in 34-75% of patients presenting with optic neuritis in the UK and USA[11].

Treatment of typical optic neuritis has been investigated in several studies, the results of which have shown that corticosteroids accelerate recovery of vision without affecting the final visual outcome[12]. Atypical optic neuritis usually requires corticosteroid therapy but often requires aggressive immunosuppression in addition[10]. In 1988, Spoor and Rockwell[13] reported excellent results in a study evaluating high-dose intravenous (IV) steroids for the treatment of optic neuritis, and the optic neuritis treatment trial (ONTT) was initiated following this report. The ONTT was designed to help answer whether treatment with oral or IV steroids improves vision or improves vision more quickly after acute optic neuritis. One group received high-dose IV methylprednisolone followed by oral steroids, the second group received low-dose oral steroids only, and the third group received placebo. The results show that 3 days of high-dose IV methylprednisolone did not alter the overall visual acuity results after 6 months, but did accelerate visual recovery after optic neuritis. However, lower dose oral steroids increase the incidence of recurrent optic neuritis for reasons that remain unclear. In addition, contrast sensitivity, visual fields, and color vision in the ONTT group showed sustained improvement after 6 months compared to placebo in the IV methylprednisolone group. The treatment protocol for a typical optic neuritis attack in ONTT was to give 250 mg methylprednisolone IV four times daily, totaling 1000 mg, followed by oral steroid reduction (1 mg/kg/day for 11 days). ONTT provides the literature with the basis for evidence-based discussions on treatment and prognosis[14].

The aim of this study is to evaluate the etiological data, demographic characteristics, long-term follow-up results and prognostic factors related to final visual acuity of patients diagnosed with typical optic neuritis and treated according to the ONTT treatment protocol by presenting real-life data.

MATERIALS AND METHODS

This study adhered to the principles of the Declaration of Helsinki and was approved by Trakya University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee (desicion no: TÜTF-GÖBAEK 2024/28, date: 05.02.2024). The rights of all participants were protected, and written informed consent was obtained from the participants before the procedure according to the Declaration of Helsinki.

In the study, the files of patients who were treated with the treatment protocol recommended by ONTT, considering them to have typical optic neuritis in a tertiary ophthalmology clinic, were retrospectively reviewed. 106 patients who received

treatment with the current diagnosis between January 2010 and June 2023 were included in the study. The patients' ages, genders, and the eye from which the attack occurred were recorded. The best corrected visual acuities (BCVA) of all patients were evaluated before treatment and at 10 days, 1-3.6, and 12 months after treatment and at the last follow-up visit. BCVA at the first application was recorded as the initial BCVA, and BCVA at the last visit was recorded as the final BCVA. The study included patients with at least 12 months of follow-up. All patients underwent detailed biomicroscopic and fundoscopic examinations, and intraocular pressures were measured and noted using an applanation tonometer.

All patients included in the study were questioned about the presence of diagnosed MS disease. In the current optic neuritis attack, the neuritis types observed in the fundoscopic examination, including anterior optic neuritis accompanied by optic disc edema and retrobulbar optic neuritis without optic disc edema, were noted. The presence of a relative afferent pupillary defect (RAPD) at the time of the attack was examined. The presence of a visual field defect in the perimetry test performed at the first application and the type of defect (scotoma, altitudinal defect or concentric constriction) were recorded. All patients who were decided to have typical optic neuritis were hospitalized and received IV methylprednisolone treatment. As maintenance treatment, oral steroids were tapered off, and it was observed that the duration of oral steroid tapering was longer in some patients, and this period was grouped as shorter than 1 month and longer than 1 month and recorded. Which of these parameters had an effect on the final BCVA was examined.

Patient Selection

Inclusion criteria for the study:

Symptoms present for less than 1 week

Complaints of unilateral, sudden loss of vision or loss of contrast sensitivity

Full Ophthalmological Examinations Available

For the eye with the complaint, absence of any previous trauma or ocular surgery.

Absence of signs and symptoms suggestive of atypical optic neuritis (no increased pain with eye movements or hemorrhages in the optic nerve head or peripapillary area)

Absence of systemic or infectious diseases that may accompany atypical optic neuritis

Treatment Protocol

All patients were treated as recommended by ONTT for typical optic neuritis. Hospitalized patients were treated with 250 mg methylprednisolone 4 times a day (06:00-12:00-18:00-00:00) for 3 days, and a total of 1000 mg methylprednisolone IV per day. On the morning of the 4th day, the patients were discharged with a 1mg/kg oral steroid treatment as maintenance treatment. During this treatment process, the dose was reduced considering the visual gain and oral steroids were gradually discontinued.

Statistical Analysis

Statistical analyses were performed using IBM SPSS (IBM, USA) version 20.0. The Kolmogorov-Smirnov test was used to assess the normality of the data. For numerical descriptive statistics, normally distributed variables were presented as means and standard deviations. Descriptive statistics for categorical variables were presented as percentages. Chi-square test was used to compare categorical data. The relationship between numerical variables was assessed using the Pearson correlation coefficient test. The significance level was accepted as $p<0.05$.

RESULTS

Of the patients included in the study, 61 were female (57.5%) and 45 were male (42.5%). The mean age of the patients was 32.25±12.79 years. When the eyes with attacks were examined, 57 were right eyes (53.7%) and 49 were left eyes (46.3%) (Table 1).

The patients included in the study were consulted by the Neurology unit during hospitalization and it was seen that there were 14 patients who had MS diagnosis or were diagnosed at the time of the attack. This corresponded to 13.2% of the patients. In 65 patients (61.3%), a visual field defect was present in the perimetry test performed at the time of the attack. When these visual field defects were grouped within themselves, it was seen that 28 (26.4%) had scotoma, 17 (16%) had altitudinal defect and 20 (18.9%) had concentric narrowing. The number of optic neuritis attacks detected in the form of anterior optic neuritis accompanied by optic disc edema seen in fundoscopic examination was 67 (63.2%) and the number of those detected in the form of retrobulbar optic neuritis without optic disc edema was 39 (36.7%). RAPD was found to be positive in 56 patients (52.8%) and negative in 50 patients (47.2%) (Table 2).

The mean BCVA of the patients at the time of the attack was determined as 0.33±0.41 (0.003-1.0), while the mean final BCVA was determined as 0.65±0.38 (0.05-1.0). The patients' age, gender, side of the eye experiencing the attack, whether or not they were diagnosed with MS, presence/absence of

Table 1. Demographic features of the patients

Female/Male	61 (57.5%)	45 (42.5%)
Right eye/Left eye	57 (53.7%)	49 (46.3%)
Mean age (year)	32.25±12.79 (18-50)	

Table 2. Optic neuritis attack presentation findings of the patients	
Existence of MS	14 (13.2%)
Presence of visual field defect	65 (61.3%)
Type of visual field defect	Scotoma: 28 (26.4%) Altitudinal defect: 17 (16%) Concentric narrowing: 20 (18.9%)
Optic neuritis form	Anterior: 67 (63.2%) Retrobulbar: 39 (36.7%)
RAPD	Yes: 56 (52.8%) No: 50 (47.2%)
MS: Multiple sclerosis, RAPD: Relative afferent pupillary defect	

Table 3. Initial and final BCVA of patient subgroups	
MS	**BCVA**
Yes (14)	Initial 0.24±0.24 (0.001-0.70) Final 0.67±0.37 (0.02-1.0)
No (92)	Initial 0.33±0.33 (0.001-1.0) Final 0.65±0.39 (0.001-1.0)
MS: Multiple sclerosis, BCVA: Best-corrected visual acuity	

visual field defect or its type if any, type of optic neuritis attack, initial BCVA, and the rate of discontinuation of oral steroids (longer or shorter than 1 month) were evaluated in terms of their effects on the final BCVA (Table 3). It was found that two parameters had a statistically significant effect on the final BCVA. The first of these was the initial BCVA, and it was found that the high initial BCVA was positively correlated with the final BCVA (p=0.01). In addition, it was found that the previous optic neuritis attack being retrobulbar optic neuritis was a positive factor on the final BCVA (p=0.04).

DISCUSSION

This study evaluated the demographic characteristics, clinical findings, and long-term visual acuity of patients diagnosed with typical optic neuritis, characterized by inflammation of the optic nerve, and treated according to the ONTT protocol, and the prognostic factors affecting these results. The study findings are consistent with previous literature showing that optic neuritis is more common in young adults and female patients[1,4,7,15]. The proportion of female patients in this study was 57.5%, which is in line with previous epidemiological studies. Similarly, a single-center study was recently conducted in a tertiary hospital in Eastern India to determine the clinical and demographic profile of optic neuritis, and it was reported that 64.3% of patients diagnosed with optic neuritis were female[16].

In this study, a significant relationship was found between initial BCVA and final BCVA. It was observed that high initial BCVA had a positive effect on the long-term visual acuity of the patients (p=0.01). This finding suggests that, as reported in previous studies, early detection of visual acuity in optic neuritis patients may be a determining factor in terms of long-term prognosis[17]. Küchlin et al.[18] reported that they examined clinical predictors in acute optic neuritis and concluded that being older, being male, and having worse visual function at the beginning posed a risk for worse clinical outcomes. This study also predicts that the higher the initial BCVA, the better the final BCVA, in line with the literature; however, no clinically significant correlation was observed between age and gender and final BCVA. This study also found that patients with an attack of retrobulbar optic neuritis had a better visual prognosis than patients with anterior optic neuritis (p=0.04). This may suggest that retrobulbar optic neuritis may generally be associated with milder inflammatory processes.

When examined in terms of visual field defects, 61.3% of the patients in this study had any visual field defects detected in the perimetry test. Different patterns such as scotoma, altitudinal defect and concentric narrowing were observed. In the study published by ONTT, it was reported that 68.8% of the optic neuritis patients they followed had visual field involvement at the beginning, 48.2% of them had diffuse visual field loss, 8.3% had central or centrocecal scotoma, 20.1% had altitudinal or other nerve fiber bundle type defects and 23.4% had various other defects[19]. Similar visual field defects have been reported in patients with optic neuritis in previous studies[20]. This finding emphasizes that optic neuritis has different effects on the optic nerve and that patients' visual field losses should be taken into account in clinical management. In a study, it was shown with electrodiagnostic evidence [visual evoked potential (VEP)] that the combined corticosteroid regimen recommended by ONTT improved conduction in the visual pathways of patients with first-attack optic neuritis earlier than conservative treatment[21]. In this study, the patients' VEP results were not evaluated because they could not be accessed completely.

In addition, in this study, the ONTT protocol was applied and a significant improvement in visual acuity was observed in the majority of patients treated with this protocol. ONTT was a multicenter randomized clinical trial that was established in the 1980s in the USA with the support of the National Eye Institute and developed to evaluate corticosteroid treatment for optic neuritis. Four hundred fifty-seven patients were included in the ONTT study between 1988-1991 and the first report was reported in the 6th month[22], and the last examinations were made in 2006 and the results of approximately 15 years were published[23]. It is stated that the dose adjustments of corticosteroids in the ONTT study were selected based on data currently used in clinical practice when designing the study[24,25]. The ONTT results showed that IV high-dose methylprednisolone accelerated early visual recovery but had no significant effect on final visual acuity[26]. In this study, similar to the results of the ONTT study, the majority of patients showed improvement

in visual acuity after treatment. However, the effect of steroid treatment on long-term MS development is still controversial, and in the study reporting ONTT results, it was stated that only low-dose oral steroid use may temporarily increase the risk of optic neuritis recurrence[23]. Therefore, future studies can evaluate the long-term results of treatment protocols more comprehensively. According to the same study, those receiving IV corticosteroids followed by oral corticosteroids have a temporary lower risk of developing a second demyelinating event consistent with MS compared to subjects treated with oral placebo or oral corticosteroids alone[23]. In light of this information, the rationale for implementing the treatment protocol recommended in the ONTT is primarily based on the aim of rapidly reversing vision loss, suppressing inflammation, and preventing relapses and possible neurological progression in the long term. Future studies may evaluate the long-term outcomes of treatment protocols more comprehensively.

In a study conducted by Rodriguez et al.[27] to determine the prevalence and incidence of optic neuritis, the rates of optic neuritis patients developing MS were also evaluated and it was determined that 39% of the patients progressed to clinically definite MS in a 10-year follow-up. It was also reported that 49% of the patients progressed to MS in 20 years, 54% in 30 years and 60% in 40 years. In this study, 13.2% of the patients had a diagnosis of MS. While the lack of communication between the patients in their neurology consultations may be the reason for this, the lack of sufficient follow-up periods may also be considered as another reason.

Study Limitations

This study has some limitations. First of all, due to the retrospective nature of the study, data were obtained from past records, which may have caused some clinical and demographic information to be missing. Follow-up periods, long-term activations, or MS diagnoses that may have been received later in another center may have been missed. In addition, since patient selection was made based on existing recorded data, the possibility of selection bias in the sample cannot be ruled out. The lack of standardization of clinical data at the time of initial recording also increases the risk of information bias. Considering all these limitations, prospective studies with large patient populations are needed to obtain more information about the clinical course of optic neuritis, response to treatment, and factors affecting prognosis.

CONCLUSION

In conclusion, the data obtained in this study support the effectiveness of the ONTT treatment protocol in patients with typical optic neuritis. The female predominance and the mean age of 32.25 years are consistent with previous reports. Initial BCVA and retrobulbar form of optic neuritis were determined as positive factors in terms of long-term visual prognosis. However, it is thought that long-term follow-up and treatment options of patients who may have MS should be examined in more detail.

Ethics

Ethics Committee Approval: This study adhered to the principles of the Declaration of Helsinki and was approved by Trakya University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee (desicion no: TÜTF-GÖBAEK 2024/28, date: 05.02.2024).

Informed Consent: The rights of all participants were protected, and written informed consent was obtained from the participants before the procedure according to the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.C.Ç., A.K.Ç., A.K.S., R.G., E.K., H.G., Concept: A.C.Ç, A.K.Ç., A.K.S., R.G., E.K., H.G., Design: A.C.Ç, A.K.Ç., A.K.S., R.G., E.K., H.G., Data Collection or Processing: A.C.Ç, A.K.Ç., A.N.M.D., T.B., Analysis or Interpretation: A.C.Ç., A.K.Ç., Literature Search: A.C.Ç., A.K.Ç., A.N.M.D., T.B., A.K.S., R.G.,E.K., H.G., Writing: A.C.Ç., A.K.Ç.

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