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Short term outcomes of the use of high dose intravenous methylprednisolone for acute optic neuritis in a central Anatolian population

Aim: To describe the clinical characteristics and outcome of optic neuritis (ON) cases treated with high dose intravenous methylprednisolone (IVMP) in a tertiary referral clinic in Ankara, Turkey.

Methods: Consecutive patients in the past 5 years with acute isolated ON, who were treated with IVMP and had a follow–up of at least 3 months, were reviewed. Symptoms and findings, results of brain magnetic resonance imaging (MRI), etiologies, visual outcomes, and side effects of the treatment were evaluated.

Results: Etiological causes could be elicited in 57 (85.1%) of 67 patients; the most common of which was multiple sclerosis (MS). At least 1 MS–compatible white matter lesion was present on brain MRI in 31 (46.3%) patients. Seventeen (63.0%) of those with clinically definite MS (CDMS) had ON as the initial feature of their disease (25.4% of all patients). Early treatment was associated with better short term visual outcomes. Diagnosis of MS was more possible in patients with retrobulbar neuritis and MS patients achieved better short term visual outcomes than non-MS patients with IVMP.

Conclusion: The majority of our cases were associated with MS and evidence from our study confirmed the short term benefit of the standard therapy in our population.

Key words: Acute optic neuritis, high dose intravenous methylprednisolone, multiple sclerosis

Orta Anadolu popülasyonunda intravenöz yüksek doz metil prednizolon ile akut optik nevrit tedavisinin kısa dönem sonuçları

Amaç: Ankara'daki üçüncü basamak tedavi merkezinde yüksek doz intravenöz metilprednizolon (İVMP) ile tedavi edilen optik nevrit (ON) hastaların klinik özelliklerini ve sonuçlarını tanımlamak.

Yöntem ve gereç: Geçmiş 5 yıl içinde akut izole ON nedeniyle İVMP tedavisi uygulanan ve en az 3 aylık takibi bulunan hastalar gözden geçirildi. Semptomlar ve bulgular, kranial manyetik rezonans görüntüleme (MRG) sonuçları, etyolojik nedenler, görme sonuçları ve tedavinin yan etkileri değerlendirildi.

Bulgular: Çalışma kriterlerine uyan 67 hastanın 57sinde (% 85,1) etyolojik neden tespit edilebildi. En sık karşılaşılan etyolojik neden multipl sklerozdu (MS). Otuz bir hastanın (% 46,3) beyin MRG'sinde en az 1 adet MS ile uyumlu beyaz cevher lezyonu tespit edildi. Kesin MS tanısı konanların 17'sinde (% 63,0) ON başlangıç bulgusuydu (tüm hastaların % 25,4'ü). Erken tedavi, erken dönem görme prognozunu olumlu etkiledi. Retrobulber nevrit tanısı ve İVMP tedavisi sonrası daha iyi görme keskinlikleri MS ile ilişkili bulundu.

Sonuç: Hastalarımızın büyük bir çoğunluğu MS ile uyumluydu ve çalışmamızın sonuçları standart tedavinin kısa dönem faydalarını doğruladı.

Anahtar sözcükler: Akut optik nevrit, yüksek doz intravenöz metilprednizolon, multipl skleroz

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Introduction

Optic neuropathy is a wide definition that comprises primary demyelination or non-demyelinating disease of optic nerve. The term optic neuritis (ON) is usually used for primary demyelinating events, such as the optic neuropathy associated with multiple sclerosis or idiopathic conditions (1). The most common

cause is optic nerve demyelination and the association between ON and demyelinating disease is well established. It commonly occurs as an isolated neurological finding and may represent a forme fruste of multiple sclerosis (MS) (2,3).

Studies related to ON have been ongoing in western countries. In USA, the optic neuritis treatment trial (ONTT) is a randomized, multi centered, placebo-controlled clinical trial (3,4). Also, there are some reports describing the epidemiological and clinical features of ON from different Asian countries (5-8). However, we are not aware of any longitudinal studies in Middle–Eastern countries, and there is only one similar study from Turkey in the literature (9).

In the present study, we aimed to describe the clinical features, etiology and visual outcomes of patients with ON who were treated with high dose intravenous methylprednisolone (IVMP) in our tertiary eye clinic in Ankara, Turkey.

Materials and methods

This study was a retrospective, observational case series involving 67 patients with acute

isolated optic neuritis (ON) who were hospitalized, evaluated with brain magnetic resonance imaging (MRI), treated with high dose intravenous methylprednisolone (IVMP), and followed for at least 3 months. Clinical data were abstracted from the last 5 years' patient charts of the Neuro-ophthalmology Department.

Symptoms and a complete neuro-ophthalmic examination were recorded. Best corrected distance visual acuity (VA) (Snellen's chart), color vision (CV) (Ishihara's color vision plates), relative afferent pupillary defect (RAPD) (swinging flashlight test), fundoscopy (dilated pupil-90 D lens), and visual fields (VF) (Humphrey ® Field Analyzer or confrontation) were evaluated. Decision for treating each patient with IVMP was made solely on clinical basis; taking into account the visual, medical, and social conditions of the patient at the initial examination. Therapy was started immediately after a total blood count, blood chemistry test, and a chest X-ray. All patients were hospitalized and received IVMP 1000 mg/day as a single dose or in 4 divided doses for 3 days. Pulse rate and blood pressure were monitored during intravenous infusion therapy. Serum electrolytes and blood sugar (fasting and postprandial) were evaluated before and after treatment. Thereafter, therapy was continued with an oral prednisolone equivalent dose of 1mg/kg/day for 11 days and then the dose was tapered to be discontinued in the third week. Adverse effects of the treatment were recorded during and after hospital stay.

Brain MRI was performed before or during hospital stay. Other laboratory tests and consultations were carried out as needed. Aforementioned ophthalmic parameters were evaluated daily during the period of intravenous treatment. Afterwards, patients were examined during week 1, 4, and 12. From then on, at least 1 final follow-up visit was scheduled.

Descriptive statistics were used for evaluating the data. Statistical analyses were carried out using SPSS 9.0 with Pearson Chi-Square Test and Fisher's Exact Test.

Results

Seventy six eyes of 67 patients were evaluated. Of the 67 patients, 16 (23.9%) were male and 51 (76.1%) were female. Mean age was 29.0 ± 10.8 years (7 to 51 years). Demographic features and clinical summary of the patients are summarized in Tables 1 and 2.

Table 1. Demographic features of the patients.

Sex	No of patients (%)	Mean age
Female	51 (76.1)	27.5 ± 11.8
Male	16 (23.9)	29.4 ± 10.5

Table 2. Types of involvement of optic nerve head.

	No of patients (%)		
	Anterior	Retrobulbar	Total
Unilateral	12	46	58
Bilateral	8	1	9
Total	20 (29.9)	47 (70.1)	67 (100)

Twenty seven of our patients (40.3%) had pain with ocular movements and retrobulbar or supraciliary discomfort before or during visual loss. Among these; 17 were diagnosed with MS (63.0%). Of patients who did not complain of pain upon eye movements, 42.5% were diagnosed with MS. The difference was obvious but not statistically significant (P = 0.060). Pain was relieved in the first 24 h in all patients during IVMP therapy.

Retrobulbar neuritis was diagnosed in 47 patients (70.1%) in our study group. Among these; 28 were diagnosed with MS. Of other 20 patients with optic disc swelling (papillitis), 6 were diagnosed with MS. This difference was statistically significant (P = 0.034).

At the initial examination, 4 eyes (5.3%) had no light perception, 54 eyes (71.0%) had light perception to finger counting vision. Sixty eight (89.5%) of the affected eyes had no CV at presentation. The best CV was 4/12. Confrontation VFs demonstrated diffuse central depression in 70 eyes (92.1%). Automatated perimetry revealed other types of VF defects in 6 eyes (7.9%), which included para central in 3, arcuate in 2, and altitudinal in 1. A positive RAPD was recorded in 58 charts.

Thirty one patients (46.3%) demonstrated MS-compatible plaques on the brain MRI. In 26 of these, there were more than 2 plaques. Increased signal consistent with optic nerve demyelination was also detected in 3 MS patients. In 5 patients (7.4%), multiple plaques incompatible with MS were present. These were diagnosed with central nervous system vasculitis, SLE, mitral valve prolapsus, and brain metastasis. Optic nerve demyelination was confirmed with orbital MRI in 5 unilateral cases with normal brain MRI (7.4%). Additionally, pan sinusitis was detected in 5 patients. MRI findings are summarized in Table 3.

Etiological causes could be elicited in 57 patients (85.1%) along with 10 patients (14.9%) who were classified as idiopathic. MS was the most commonly diagnosed disease. CDMS was present in 27 patients (40.3%). Diagnosis of CDMS was present before the ON attack in 10 and ON was the first attack of CDMS in 17. This means that; 25.4% of all patients and 63.0% of the CDMS patients had an ON attack as the presenting feature of CDMS. An additional 7 patients were considered as probable MS cases after neurological consultation. Other etiologic factors

Table 3. Brain MRI findings of patients (MS: Multiple Sclerosis).

No of patients	%	Brain MRI findings	
		No of patients	
			MS related plaques
		26	>2 plaques
31	46.28	2	2 plaques
		3	1 plaque
			Non-MS plaques
		3	Vasculitis
5	7.46	1	Occlusive
		1	Metastatic
5	7.46		Optic nerve demyelination Normal brain MRI
5	7.46		Pansinusitis Normal brain MRI
21	31.34		NORMAL
67	100	Total	

were found to be post-viral demyelination, vasculitides, pan sinusitis, vaso-occlusive disease, and brain metastasis (Table 4).

Time to treatment with IVMP from the first symptom was 8.3 ± 6.7 days (range 1 to 30 days). Time to treatment was 0-7 days in 39 patients (58.2%) and 8 or more days in 28 patients (41.8%). Final visual acuity was better than 0.5 in 38 (97%) of the early treated group and 21 (75%) in the late treated group. This difference was statistically significant (P = 0.028).

Adverse effects of treatment were recorded in 14 patients (21.0%) during or after therapy. These were, in decreasing frequency; sour taste in mouth, flushing and fever (during infusion); nausea, vomiting and/or stomach ache, insomnia, depression, crying episodes, transient increase in blood sugar and hepatic enzymes (shortly after infusion); and weight gain, back pain and menstrual changes (during the course of oral therapy). These side effects disappeared in a short time period after tapering of steroids.

Patients were followed for a mean of 7.86 ± 8.29 months (range 3 to 48 months). VA recovered to better than 0.5 at the end of the follow-up in 59 eyes (77.7%). In this group with good visual outcome, 22 were diagnosed with MS. Of the patients who had less than 0.5 VA at the end of follow-up, only 2 were diagnosed with MS. This difference was statistically significant (P = 0.017).

Thirty nine eyes (51.3%) regained full CV. Only 8 eyes (10.5%) remained totally color blind. VF testing was performed in 69 eyes at the end of the study. Persistent arcuate and para central field defects were found in 24 patients (34.8%). Pre and post-treatment visual functions of patients are summarized in Table 5. RAPD was not recorded in a number of patients after therapy, therefore evaluation was not possible.

At the last examination, 33 patients (49.3%) had normal-appearing optic discs and 34 patients (50.7%) had temporal optic atrophy. Two patients with CDMS had recurrent attacks in contra lateral eyes during follow-up.

Table 4. Etiological causes (CDMS: Clinically Definite Multiple Sclerosis, Dx: Diagnosis, CNS: Central Nervous System, SLE: Systemic Lupus Erythematosus).

Etiology (No of patients)		Number	%
MS related	CDMS present (10) CDMS new Dx(17) Probable MS (7)	34	50.7
Idiopathic		10	14.9
Postviral		8	11.9
Vasculitis	CNS vasculitis (2) Retinal vasculitis (1) SLE (3) Autoimmune (1) Behcet's Disease (1)	8	11.9
Pan-sinusitis		5	7.4
Occlusive		1	1.6
Brain metastasis		1	1.6
Total		67	100

Table 5. Pre and post-treatment visual statuses of patients (CV: Color Vision, CS: Central Scotoma, VF: Visual Field, VFD: Visual Field Defect).

At the initial examination			After treatment		
	No of eyes	%		No of eyes	%
Visual acuity			Visual acuity		
0.1 ↓	58	76.3	0.1 ↓	2	2.6
0.1-0.5	17	22.4	0.1-0.5	15	19.7
0.5 ↑	1	1.3	0.5 ↑	59	77.7
Color vision			Color vision		
No CV	68	89.5	No CV	8	10.5
1-6/12	8	10.5	1-6/12	14	18.5
7 -12/12	0	0	7 -12/12	54	71.0
Visual field			Visual field		
CS	70	92.1	CS	1	1.4
Other VFDs	6	7.9	Other VFDs	24	34.8
Normal VF	0	0	Normal VF	44	63.8

Discussion

We integrated all patients treated with high dose IVMP into this retrospective study; however, our patients were a heterogeneous group, which was different from the patients studied in the ONTT and other studies. The present study included children and adults, unilateral and bilateral cases, first or second attacks, people who had visual loss lasting longer than 7 days before the initiation of therapy, and people with other diseases. We keep all differences in mind, but still comparisons with ONTT and other studies help us define the clinical characteristics and response to treatment in our population.

Our local population, with a mean age of 29.0 years was slightly younger than the ONTT population (mean age: 31.8). Excluding the 4 children younger than 12 years, our population's mean age rises to 30.3 years. A median age of 30.5 years is reported from India, older median ages of 35.6 and 39.1 years are reported in Asian populations (6-8). The median age was 28 years in a Scandinavian study (10).

Seventy six percent of our patients were female. This figure is 77% in ONTT and 62% in the Scandinavian study (3,10). Women's ratio is lower in studies involving Indian (25%) and Asian (39%) populations (6,8). Our population's sex ratio resembles the ONTT population in this respect. We are not aware of any similar study involving Mediterranean or Middle-eastern demographic.

Periocular pain exacerbated by ocular movements in acute demyelinating optic neuropathy patients is reported as 50% in an Asian population and nearly 90% in ONTT (3,6). This percentage includes all (MS or non-MS) inflammatory optic neuropathies. Optic nerve inflammation is thought to cause pain by stimulating the trigeminal innervation of the optic nerve sheath (2). Pain is one of the clinical features associated with a higher risk of MS (11). Of our patients, 40.3% had pain with ocular movements and retrobulbar or supraciliary discomfort before or during visual loss. MS was more often diagnosed in patients who experienced retrobulbar or supraciliary pain, but the difference did not reach statistical significance (P = 0.060).

Normal appearing optic disc (retrobulbar optic neuritis) is another feature linked to a higher risk of MS (11). Retrobulbar ON is reported in 71% in the Scandinavians, 66% of the ONTT group, and 35 % in an Asian population sample (3,6,10). Retrobulbar neuritis was diagnosed in 47 patients (70.1%) in our study group. Among these, MS was more often diagnosed compared to the patients with papillitis (P = 0.034).

The third feature attributed to a higher risk of MS is the low VA (less than 0.5) at presentation (3). All of our patients except only 1 CDMS patient had VAs of less than 0.5. Since we retrospectively analyzed

patients who underwent IVMP therapy, evidently we did not treat patients with good vision therefore we cannot comment on VA at presentation.

After 6 months follow–up, the percent of eyes regaining full VA was 62% in ONTT and 57% and 39% in Asian studies (6,8). We achieved full VA in 41 of 76 eyes (54%). When we look at the final VAs, it appears that our MS patients had better visual outcomes than non-MS patients. Patients who had a final VA of at least 0.5 were more frequent in patients diagnosed with MS when compared to non MS patients (P = 0.017)

Color vision deficit was detected in all patients at presentation. At the end of follow–up, 8 eyes (10.5%) remained totally color blind. Mild CV abnormalities were permanent in 48.7%. More patients mentioned red desaturation and contrast sensitivity deficits, which we did not document. In ONTT and other studies, it was shown that even after maximal recovery of visual function, a subtle CV abnormality was the most common residual visual deficit (12).

The most common visual field defect at presentation was diffuse central depression (92.1%). This includes central and pericentral defects, because, due to our patients' low levels of VA, we mostly evaluated VFs by confrontation. At the final visit, 34.8% of tested eyes had residual, mostly insignificant VF defects. In ONTT, subtle VF defects persisted in 48% of patients (12).

It is reported that 40% to 70% of those who have isolated optic neuritis, periventricular white matter signal abnormalities are detected on MRI scans (2,3,10). The development of CDMS is strongly associated with the presence of 1 or more lesions on the baseline MRI of the brain (11). Up to 50% of patients with MS will develop ON and 20% of the time, ON is the presenting sign of MS (1,2,10,11). Abnormal brain MRI was obtained in 68.7% of our patients. Thirty one (46.3%) demonstrated MS-compatible demyelinating plaques. In a former Turkish study of MS patients, 53.3% of 68 patients with CDMS had evidence of a previous ON attack (13). In 63.3% of our patients diagnosed with CDMS, ON attack was the presenting feature of the disease. This percentage is noticeably high which implies that the importance of obtaining brain MRI in the first attack of ON in every patient is imperative.

Our treatment decision was only dependent on the initial clinical evaluation; therefore, we did not wait for any test results except routines to start treatment. In the ONTT, typical features of acute demyelinating ON were considered and less than 1.0% of patients were misdiagnosed. We mostly diagnosed MS, vasculitic diseases, and idiopathic or post viral inflammations, in whom we started treatment without thorough investigations. These can all be treated with IVMP. However, we seem to have mistreated the anterior ischemic optic neuropathy (AION) in cases with mitral valve prolapsus and breast carcinoma metastasis and we put these 2 patients under undue risk since IVMP is controversial in the treatment of AION.

Also, we did not respect the ONTT deadline of 7 days, and initiated treatment as late as 30 days. Time to treatment was 0-7 days in 39 patients (58.2%) and 8 or more days in 28 patients (41.8%). Final visual acuity was better in the early treated group (P = 0.028). This implies that we should not hesitate to treat with IVMP when we think appropriate as soon as we examine the patient. This is especially worth consideration in countries like Turkey where people may not have rapid access to the neuro-ophthalmologist.

Although our population sample and study parameters were not exactly similar, considering the high incidence of the CDMS diagnosis after ON and the low incidence of side effects of this therapy, we think that the ONTT guidelines can be used safely in our population and we recommend high dose IVMP with caution in patients with ON.

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