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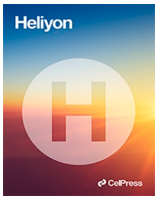

Research article

The clinical profile of new-onset optic neuritis in arabs, a tertiary center experience in Kuwait

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A R T I C L E I N F O

Keywords:
Optic Neuritis
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A B S T R A C T

Background: Optic neuritis is an inflammatory disorder of the optic nerve and is often the initial manifestation of systemic demyelinating diseases such as multiple sclerosis (MS), neuromyelitis optic spectrum disorder (NMOSD), and myelin-oligodendrocyte glycoprotein (MOG) antibody-mediated disease. There are ethnic variations in the etiology of optic neuritis across the world. While multiple sclerosis is common in the West, NMOSD and MOG are more common causes in Asian patients. There is a paucity of reports on the clinical profile of optic neuritis in the Middle East.

Objectives: To study the demographic and clinical features of patients with new onset optic neuritis in a main tertiary care center.

Methods: A retrospective study of cases with new-onset optic neuritis at a tertiary care center between 2012 and 2022. The clinical and demographic characteristics were obtained from medical records and were summarized using descriptive statistics. Univariate analysis and multivariate analysis to assess the short-term visual outcome.

Results: Seventy-one patients with new-onset optic neuritis (70 unilateral and one bilateral) were included in the study. The mean age was 33.3 years, they were predominantly females (73 %), and most of the cases were MS (53 %) followed by idiopathic optic neuritis (42.3 %). Final visual acuity of at least 20/40 was seen in at least 91.5 %.

Conclusion: While the clinical profile of patients in this study closely resembles the Optic Neuritis Treatment Trial with a high incidence of MS and a good visual outcome in most patients and a good response to intravenous steroids, there is a significant proportion of idiopathic optic neuritis cases that may need to be better characterized with longer follow up and repeated serum biomarker testing.

1. Introduction

Optic Neuritis is an acute inflammatory disorder of the optic nerve and although it can be idiopathic, is often the presenting clinical feature of neurologic demyelinating diseases, most frequently multiple sclerosis, neuromyelitis optics spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein-associated disease (MOGAD) [1–3]. The optic neuritis treatment trial (ONTT) was the

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principal trial in characterizing the clinical features, treatment, and prognosis of optic neuritis [4,5]. However, it was based on a Western white population, and overwhelmingly included patients with MS-associated optic neuritis. Several studies have shown that there are ethnic variations in the clinical features and etiology of optic neuritis [6,7]. NMOSD and myelin oligodendrocyte glycoprotein (MOG) optic neuritis are more common in Asian patients, and therefore the clinical features of Asian optic neuritis vary from classic MS-associated optic neuritis [8–10]. There are few studies on the clinical and epidemiological features of optic neuritis in Middle Eastern Arab patients. In this study, we describe the clinical features of a cohort of patients with new-onset optic neuritis in a neurology/neuro-ophthalmology tertiary care center in Kuwait.

2. Methods

We have reviewed the medical records of patients admitted to the neuroophthalmology unit in Ibn Sina Hospital diagnosed with new-onset optic neuritis from 2012 to 2022. The clinical and the demographic characteristics were obtained from medical records (Age, ender, follow up-duration, pain at onset, disc edema at onset, final diagnosis, visual acuity at onset and follow-up, dose of intravenous steroids, oral steroid taper, administration of plasma exchange or intravenous immunoglobulins, MRI T-2 and gadolinium-enhancing brain lesion, MRI optic nerve lesions, presence of oligoclonal bands in the CSF, final mean deviation of the visual field, and the final OCT peripapillary retinal nerve fiber layer thickness).

The diagnosis of optic neuritis was made based on the clinical features of acute vision loss, afferent pupillary defect in unilateral cases, and a decrease in visual acuity or color vision and a visual field defect. All patients did not have any previous neurological disease, or prior history of optic neuritis or other optic neuropathy. All patients had MRI of the brain and orbit and appropriate laboratory tests, including oligoclonal bands (OCB) in cerebrospinal fluid (CSF) serum antibodies for aquaporin-4 immunoglobulins (AQP4-IgG) and MOG as appropriate in cases with atypical features of MS-optic neuritis, such as bi-laterality, severe visual loss at

Table 1
Clinical characteristics for all cases of optic neuritis.

Age (mean ± SD) in years		(33.3 ± 9.2)
Age Categories	16–26 years	16 (22.5 %)
	27–38 years	39 (55 %)
	39 years and older	16 (22.5 %)
Gender	Female	52 (73.2 %)
	Male	19 (26.8 %)
Follow-up duration (months)	20.46 ± 29.83	
Pain at onset	Painful	55 (77.5 %)
	Painless	16 (22.5 %)
Disc Edema	Present	35 (49.3 %)
	Absent	36 (50.7 %)
Type of ON	Idiopathic ON	30 (42.3 %)
	MS-ON	38 (53.5 %)
	NMO-ON	2 (2.8 %)
	MOG-ON	1 (1.4 %)
MRI Optic Nerve lesion	None	30 (49.2 %)
	Unilateral	29 (47.5 %)
	Bilateral	2 (3.3 %)
MRI T2 lesion	Single	23 (39.7 %)
	Multiple	29 (50 %)
Gadolinium-enhancing brain lesions	47 (77 %)	
Duration of follow-up in months (mean ± SD) rowhead	(20.5 ± 29.8)	
IV Steroid duration	3-days	32 (45.1 %)
	5-days	39 (55.9 %)
Oral steroid	Taper	38 (53.5 %)
	No Taper	33 (45.6 %)
Repeat IV steroid therapy	MS	7 (9.8 %)
	Idiopathic	5 (7 %)
Oral steroid taper duration (range, mean) ± SD	(3–180, 23.9) days ± 29.1	
Plasma Exchange	1 (1.4 %)	
Logmar Visual Acuity of the Affected Eye (mean ± SD)	Onset	1.51 +- 0.92
	Follow Up	0.22+-0.71
Final Visual Field MD Follow-Up	−13.2 (±12.52)	
Final Visual Acuity in the affected eye	Better or equal to 20/40	65 (91.5 %)
	Better or equal to 20/20	47 (66.2 %)

Data are expressed as the number (percentage) of patients unless otherwise specified.
SD = standard deviation.
MS = Multiple sclerosis.
NMO=Neuromyelitis Optica.
MOG = Myelin oligodendrocyte glycoprotein.
ON= Optic neuritis
MD = mean deviation.

onset, or poor response to steroid therapy. Patients with a diagnosis of multiple sclerosis met the revised 2010 and 2017 McDonald's criteria [11,12]. All patients who have had optic neuritis since 2017 were tested for AQP4-IgG and MOG antibodies. The minimum follow-up period to assess the visual outcome was 30 days following treatment of intravenous (IV) steroids. Patients were classified as idiopathic optic neuritis (if the MRI did not show lesions fulfilling the McDonald criteria for MS and had negative serology for AQP4-IgGand MOG antibodies and did not fulfill the criteria of seronegative NMOSD. MS-associated optic neuritis was diagnosed in cases in which the MRI features fulfilled the McDonald criteria at onset or during follow-up. NMOSD-optic neuritis and MOG-optic neuritis were diagnosed based on the results of serum testing for AQP-4 or MOG antibodies using commercial cell-based assays [13]. All patients received initial IV methylprednisolone treatment for 3 or 5 days with or without oral steroid taper, followed by repeat IV steroid pulse therapy, plasma exchange (PLEX), or intravenous immunoglobulins (IVIG) if indicated in case of inadequate response to IV steroid therapy. Presenting and final high-contrast Snellen visual acuity were converted into logmar units, where also counting fingers (CF) was converted to 2.6 units, hand movements were converted to 2.9 units, light perception was converted to 3.1 units, and no light perception was converted to 3.4 units. In one case where a subject had bilateral MOG-optic neuritis where the visual acuity at presentation and follow up were nearly identical, so the average logmar visual acuity of the two eyes at presentation and follow-up was used in the analysis.

A descriptive statistical analysis was performed to include means for continuous variables and percentages for categorical ones. The Mann-Whitney U and Wilcoxon signed-rank tests were used to compare the means of categories of optic neuritis related data for the final logmar visual acuity. Multiple linear regression analysis was used to determine if any of the variables were associated with the final logmar visual acuity. A p value of 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics (version 29.0). This was a retrospective observation study which received an expedited review and a waiver by the local research ethics committee of the hospital, and it was conducted in accordance with the declaration of Helsinki for research bioethics.

3. Results

Our study included 71 patients, of whom 70 had unilateral and one bilateral optic neuritis. The mean age of patients in this study was 33.3. (standard-deviation ± 9.2) years, and they were predominantly females (73 %). The age range was 16–54 and the highest incidence of optic neuritis (55.5 %) occurred in the age between 27 and 38 years (Table-1, Figure-1). The final mean logmar visual acuity in the affected eye was 0.22, and over 90 % of patients had a final visual acuity of at least 20/40, while 66 % had a final visual acuity of at least 20/20 or better in one or both eyes. (Table 1). Pain with eye movement at onset was seen in 77.5 % of patients, and about half of cases had clinically detectable optic disc edema. The most common cause for optic neuritis was MS is (53 %), followed by idiopathic optic neuritis (42.3 %), whereas NMOSD (2.8 %) and MOG (1.4 %) were the least frequent (Figure-2). IV pulse steroid therapy was given for five days in 55.9 % of cases and three days in 45.1 % of cases. An oral steroid tapering regimen was prescribed in 53.8 % of cases for a mean period of 29.1 days. PLEX was given for only one patient with MS and progressive optic neuritis in which visual acuity at onset was 20/80, and despite PLEX, his final visual acuity in the affected eye was hand motion.

About 50.8 % of patients had MRI lesions of the optic nerve, 80 % of patients had MRI T2 lesions of the brain, and 77 % of patients had gadolinium-enhancing brain lesions.

There was no significant difference in the final logmar visual acuity between males vs. females (0.09 vs. 0.26, $p = 0.7$), the presence of pain vs. no pain (0.15 vs. 0.43, $p = 0.18$), the presence of disc edema vs. no disc edema (0.37 vs. 0.06, $p = 0.12$), IV steroid dose of five days vs three days (0.8 vs. 0.33, $p = 0.15$), or whether oral steroid taper was given vs no taper (0.1 vs. 0.23,$p = 0.15$) . (Table 2) Patients with MS-optic neuritis had a significantly worse final logmar visual acuity in the affected eye than those with idiopathic-optic neuritis (0.95 vs 0.07, $p = 0.03$) (Table 2). There were two patients with NMOSD-optic neuritis in this study; both improved with IV steroid therapy and neither had any disc edema at the onset. The only MOG-optic neuritis case had bilateral involvement and responded to IV steroid therapy with oral steroid taper. Only five patients had a final visual acuity worse than 20/40 in at least one eye, all of whom were MS-optic neuritis patients.

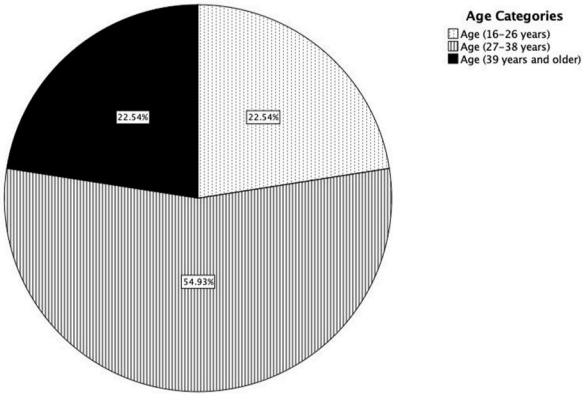

Fig. 1. A pie chart showing the distribution by percentage of optic neuritis based on different age categories of patients in this study.

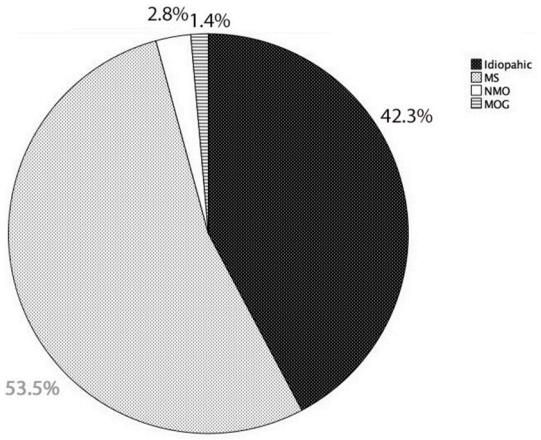

Fig. 2. A pie chart showing the etiology of optic neuritis in this study by percentage.

Table 2
The mean final logmar visual acuity comparison between different categories of optic neuritis patients.

		Final logmar visual acuity of the affected eye	p-value
Gender	Male	0.09 ± 0.17	0.9
	Female	0.26 ± 0.82	
Pain	Painful	0.15 ± 0.51	0.18
	Painless	0.43 ± 1.2	
Disc Edema	Present	0.37 ± 0.97	0.12
	Absent	0.06 +- 0.17	
IV Steroids dose	3-days	0.33 ± 0.93	0.15
	5-days	0.08 ± 0.18	
Type of ON	Idiopathic	0.04 ± 0.07	0.03 *
	MS-ON	0.4 ± 0.95	
Oral steroid taper	Yes	0.11 ± 0.2	0.70
	No	0.34 ± 1.0	
MRI Optic Nerve lesion	Absent	0.12 ± 0.49	0.15
	Present	0.15 ± 0.23	

Mann-Whitney *U* test was used, and a p-value of 0.05 was considered significant.
ON= Optic neuritis
MS = Multiple sclerosis.

Twelve patients needed repeat IV pulse steroid therapy courses; five of them had idiopathic optic neuritis, and seven had MS-optic neuritis. There was no difference between patients treated with repeat vs. single pulse IV steroids in the initial visual acuity (1.6 vs. 1.5 logmar units, $p = 0.65$) nor the final visual acuity (0.5 vs. 0.7 logmar units, $p = 0.7$).

Finally, multivariable linear regression analysis showed that the final Logmar visual acuity was not significantly associated with the diagnosis ($p = 0.45$), pain ($p = 0.6$), disc edema ($p = 0.2$), dose of IV steroids ($p = 0.42$), oral steroid taper ($p = 0.23$),repeat IV steroid therapy ($p = 0.09$), or MRI lesions of the optic nerve ($p = 0.95$).

4. Discussion

The most common cause of optic neuritis in this study was idiopathic and MS, while NMOSD and MOG optic neuritis were infrequent. Almost half of patients were diagnosed with MS either at onset or during follow-up after fulfilling the McDonald criteria for MS. The clinical profile of optic neuritis patients in this study and similar ethnic groups reported suggest that it is similar to the ONTT [4,14]. All patients were treated with IV steroid therapy for either three days or five days with or without oral steroid taper, and there was no difference in the final visual outcome between these groups. MRI brain lesions were frequent in this study, comprising T2 lesions in 80 %, and gadolinium-enhancing lesions in 77 %. This may be explained by the relatively high prevalence of MS in subjects of this study reflecting referral bias and preferences to a tertiary care center. The diagnosis of MS was made in 53.3 % of patients either at onset or with follow-up while 42.3 % were diagnosed as idiopathic optic neuritis. n the ONTT, 50 % progressed to MS during a follow-up period of 15 years [14].While the follow-up duration of our patients (20.5 months) is significantly shorter than the ONTT, the revised current diagnostic criteria for have allowed for much earlier diagnosis of MS [12]. Studies on the clinical profile and characteristics of optic neuritis in the Middle East are few in the literature [15–17]. A retrospective study from Saudi Arabia on 60 patients showed that MRI brain lesions were seen in 55 %, and most of these patients developed MS with follow-up. There was a higher female prevalence (63.3 %), and most patients had complete visual recovery with treatment [15]. A study in Turkey found a female

predominance of optic neuritis; pain was reported in around 60 % of patients. MS-optic neuritis was the most frequent optic neuritis, while NMO-optic neuritis was the least frequent [17]. Almost 77.5 % of patients in this study had pain with eye movements at onset, which is consistent with the ONTT and studies from Saudi Arabia [4,15]. In a study in Oman on the presenting feature of MS, 28.8 % of patients presented with optic neuritis [16]. The relative high prevalence of MS in these studies from the middle east is similar to what we have seen in this study.

The crude prevalence of MS in Kuwait is 104.88 per 100,000 persons, which is more comparable to Western country prevalence and was found to be higher than other Middle Eastern countries such as the UAE, Qatar, and Iran, with a higher prevalence in women at peak age of onset for both genders in the 30–39 years age group [18]. The relative high prevalence of MS-optic neuritis in this study can also be probably attributed to the incorporation of CSF oligoclonal bands in the revised diagnostic criteria. In contrast, many of these patients would have been categorized as idiopathic-ON or clinically isolated syndrome in the past [12].

A significant percentage (42.3 %) of the optic neuritis cases in this study were idiopathic and 4.2 % were either serologically confirmed MOG or NMOSD optic neuritis. Given that AQP-4 IgG and MOG antibodies were only tested routinely after 2017 and in highly suspicious cases, it is possible that a proportion of the idiopathic patients may have been NMOSD or MOG optic neuritis cases. The sensitivity of the serum assay for AQP4-IgG and MOG antibodies have improved over recent years, and it is possible that some of the cases tested were false negatives. Furthermore, the high responsiveness to IV steroids in the overwhelming majority may suggest that at least a proportion of these may be MOG optic neuritis and may need to be identified by repeated testing and maybe longer follow up.

Two cases in this study were diagnosed as NMOSD-optic neuritis, and both responded well to IV steroids. The exact prevalence of NMOSD and MOG in the Middle East still undetermined, but it appears less common than MS. In a cross-sectional study done in Kuwait, 32 patients were diagnosed with NMOSD, of whom 81.3 % were women with a mean age of onset 35.6 years, 56.3 % were AQP4 seropositive. Fifty percent of patients in that study presented initially with optic neuritis as the initial manifestation of NMOSD [19,20]. Similarly, a retrospective multicenter observational study in Saudi Arabia of 23 NMOSD patients, 19 of whom were females (82.6 %) with a mean age of onset of 38 years, found 73.9 % AQP-4 seropositivity, and only three cases presented as optic neuritis [21].

In contrast, NMOSD and MOG are more common in Asian countries, while MS is less common. A study in Thailand found that the incidence of MS following optic neuritis was 1.8 % and the most common cause of acute ON was idiopathic (51.5 %), followed by NMOSD (30.9 %) and MOGAD (5.3 %) [22]. Similarly, studies done in Japan, Korea, and Singapore revealed that the most common etiology was idiopathic, followed by NMOSD and MOGAD [7,9,10,23]. In India, MS is also relatively uncommon cause of optic neuritis, as in one study on 203 patients, 28.08 % were positive for MOG-antibodies, 9.85 % were positive for AQP4-IgG, while only 12 patients (5.91 %) were clinically suspected MS [8].

This study is limited by its retrospective nature and selection bias from referrals to a tertiary care hospital and therefore the clinical profile of patients in this study may not necessarily reflect the clinical profile of the population. It is also not designed to study the visual outcome since the regimen of IV and oral steroids were not standardized, and the follow up period was variable. Only 11 patients out of 71 (15 %) had a follow-up period of 1 month. Although we did not routinely test for AQP-4 and MOG antibodies in all cases, they were performed routinely after 2017 and before that date in cases with high clinical suspicion and absence of typical symptoms of multiple sclerosis. Therefore, given the overlap in the clinical features between cases of idiopathic optic neuritis and NMOSD or MOG optic neuritis, it is possible that some of the cases were either seronegative or were not tested. In addition, earlier serum biomarker assays were less sensitive and some of the commercially bases assays may have not been cell-based assays.

In conclusion, the clinical profile of patients with optic neuritis in the Middle East is similar to the Western clinical profile as reported in the Optic Neuritis Treatment Trial but there was a significant proportion of idiopathic cases that may need to be better characterized with longer follow up and more targeted testing for NMOSD and MOG antibodies. The short-term visual outcome of optic neuritis seems favorable with good response to IV steroid therapy. Finally, NMOSD and MOG optic neuritis seem less frequent compared to the East Asian countries.

Financial disclosure

I declare that I have no financial conflict to disclose.

CRediT authorship contribution statement

Raed Behbehani: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Abdullah Ali:** Data curation. **Ahmed Alakool:** Data curation. **Samar Farouk:** Writing – review & editing, Validation, Data curation. **Raed Alroughani:** Writing – review & editing.

Declaration of competing interest

I have no conflict or interest to disclose in relation to the submitted manuscript.

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