ORIGINAL ARTICLE

Prognostic factors in Chinese patients with acute non-infectious optic neuritis treated with intravenous methylprednisolone and oral prednisolone

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Abstract

Objectives: Non-infectious optic neuritis (ON) in Caucasians is typically associated with multiple sclerosis (MS), and steroid treatment is optional. In Chinese patients, however, ON is often atypical and more likely to be associated with neuromyelitis optica spectrum disorder (NMOSD), for which early initiation of pulse intravenous steroid treatment is recommended. We aimed to identify factors associated with visual acuity (VA) improvement after intravenous and oral steroid treatment.

Methods: We reviewed the medical records of 64 Chinese patients (64 eyes) who presented to Hong Kong Eye Hospital between 2000 and 2019 with their first episode of acute ON and received intravenous methylprednisolone and oral prednisolone.

Results: Among all cases, 45.3% were idiopathic and isolated, 25.0% were NMOSD-related, and 17.2% were MS-related. Patients with MS-related ON were younger than patients with idiopathic or NMOSD-related ON ($p<0.01$). Greater improvement in VA was associated with worse nadir VA, greater VA improvement on day 14 of steroid treatment, and NMOSD-related ON, whereas smaller improvement in VA was associated with older age and presentation before anti-aquaporin-4 testing became available.

Conclusion: Because non-infectious ON in Chinese patients is often atypical, intravenous steroid treatment is recommended (rather than optional). Treatment outcomes have improved over the past 20 years, owing to more widespread testing for anti-aquaporin-4 antibodies and more aggressive treatment of NMOSD.

Key words: Methylprednisolone; Neuromyelitis optica; Optic neuritis; Prednisolone; Steroids

Introduction

Optic neuritis (ON) in Caucasians is typically non-infectious, caused by demyelination, and associated with multiple sclerosis (MS). In the Optic Neuritis Treatment Trial (ONTT), intravenous methylprednisolone followed by oral prednisolone was found to accelerate the recovery of visual loss without altering the final visual acuity (VA). Oral steroid treatment alone (at the ONTT dose) was ineffective and increased the risk of recurrence.[1] However, neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated

disorder (MOGAD) have been increasingly recognized in patients with ON. A subsequent analysis of patients from the ONTT cohort showed that none of the serum samples was positive for anti-aquaporin-4 (AQP4) antibody and only 1.7% were positive for myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) antibody. In Chinese patients, ON is more likely to be associated with NMOSD, which requires intravenous steroid treatment. Therefore, the applicability of the ONTT protocol to the Chinese population is questionable.[2-4]

Anti-AQP4 and MOG-IgG serology tests commonly require a few days before results are available. Most cases of ON occur in seronegative patients and remain idiopathic. At the time of initial presentation, clinicians must decide whether to prescribe intravenous steroid treatment without clear information regarding the disease etiology. In our hospital, we routinely offer intravenous steroid treatment to patients with acute non-infectious ON. In this retrospective study, we aimed to identify factors associated with good visual recovery after intravenous steroid treatment.

Methods

We retrospectively reviewed the medical records of patients who presented to Hong Kong Eye Hospital between January 2000 and December 2019 with a diagnosis of ON. Inclusion criteria were age ≥12 years at presentation, Chinese ethnicity, first episode of non-infectious ON, symptom onset within 30 days of initial presentation, and completion of treatment with intravenous methylprednisolone 1 g/day for 3 days followed by oral prednisolone 1 mg/kg/day for 11 days (in accordance with the ONTT protocol). Patients with incomplete medical records, uncertain diagnosis, diagnosis other than non-infectious ON, or treatment other than the ONTT protocol were excluded.

Only one eye per patient was included in the analysis. For patients with bilateral ON, the first presenting eye was chosen. For cases with bilateral simultaneous presentation, the eye with worse nadir VA was included. In cases of simultaneous presentation where both eyes exhibited identical nadir VA, the right eye was included. VA was measured using the Snellen chart and converted to logMar units. VA of counting fingers, hand motion, light perception, and no light perception were regarded as logMAR values of 1.8, 2.3, 2.8, and 3.0, respectively.[5] VA at different time points was retrieved from patients' records; these included nadir VA, VA at the end of the 14-day ONTT protocol, and VA at the final follow-up. Associations between VA outcomes and various factors (age at onset, etiology, presentation date, and time from symptom onset to initiation of intravenous steroid treatment) were examined.

Statistical analyses were performed using SPSS (Windows version 24.0; IBM Corp, Armonk [NY], United States). For parametric data, differences among multiple groups were evaluated using one-way analysis of variance with Bonferroni correction. Multiple linear regression was used to identify factors associated with final VA improvement.

Results

Of the 133 patients with ON, 42 did not receive intravenous steroid treatment, 13 had a questionable diagnosis, eight had non-Chinese ethnicity, three had symptom onset >30 days prior to presentation, two received steroid treatment for other reasons before presentation, and one had incomplete data. The remaining 64 patients were included in the analysis.

The mean age of the 64 patients was 41.4±15.0 years; 67.2% were women. Most patients had unilateral ON (n=46, 71.9%), experienced ocular pain (n=28, 43.8%), and had disc swelling at presentation (n=22, 34.4%). The most common etiology was idiopathic (n=29, 45.3%), followed by NMOSD-related (n=16, 25.0%), MS-related (n=11, 17.2%), post-vaccination/post-viral (n=5, 7.8%), acute demyelinating encephalomyelitis–related (n=2, 3.1%), and MOGAD-related (n=1, 1.6%) [**Table 1**]. Among the 16 patients with NMOSD-related ON, five (31.3%) were seronegative. The mean logMAR nadir VA was 1.60±0.92 (approximate Snellen VA 20/800). The mean VA on day 14 (upon completion of the ONTT protocol) was 0.74±0.74 (approximate Snellen 20/100) and at the final visit was 0.47±0.79 (approximate Snellen 20/60). The median duration from symptom onset to presentation was 6 days (interquartile range [IQR]=2.25-10 days). The median time from presentation to initiation of steroid treatment (ONTT protocol) was 1 day (IQR=0-6 days). The median duration of follow-up was 3.26 years (IQR=1.73-6.73 years).

Comparison of the three largest subgroups (idiopathic, NMOSD-related, and MS-related ON) revealed that patients with MS-related ON were younger than patients with idiopathic ON (p=0.002) or NMOSD-related ON (p<0.001).

Patients were stratified according to presentation before or after March 2011, when our hospital began providing routine testing for anti-AQP4 antibodies. Multiple linear regression analysis showed that greater improvement in final VA was associated with worse nadir VA (β=0.532, p<0.001), greater VA improvement on day 14 of the ONTT protocol (β=0.335, p=0.007), and NMOSD-related ON (β=0.383, p=0.030), whereas smaller improvement in final VA was associated with older age (β= -0.015, p=0.003) and presentation before anti-AQP4 antibody testing became available (β= -0.738, p<0.001; adjusted R^2=0.721, p<0.001) [**Table 2**].

There were no major adverse effects or mortality after intravenous steroid treatment. One patient had steroid-induced central serous chorioretinopathy, another had transient ocular hypertension, and two patients had steroid-induced temporary hyperglycemia necessitating hypoglycemic agents.

Eight patients underwent plasmapheresis because of a poor response to initial steroid treatment; they were

Table 1. Clinical characteristics of 64 Chinese patients with optic neuritis by etiologies

Etiology	No. (%) of patients	No. (%) of women	Age at presentation, y*	Visual acuity*			Follow-up duration, y*
				Nadir	Day 14	Final	
Idiopathic	29 (45.3)	18 (62.1)	43.5±15.0	1.68±0.97	0.89±0.78	0.58±0.85	2.49
Neuromyelitis optica spectrum disorder–related	16 (25.0)	15 (93.8)	48.4±11.0	1.78±0.91	0.93±0.81	0.68±1.02	3.34
Multiple sclerosis–related	11 (17.2)	7 (63.6)	29.7±8.0	0.99±0.63	0.35±0.47	0.08±0.09	3.21
Post-vaccination/post-viral	5 (7.8)	3 (60.0)	39.1±23.1	1.64±1.15	0.46±0.58	0.25±0.25	2.86
Acute demyelinating encephalomyelitis–related	2 (3.1)	2 (100)	29.8	2.04	0.15	0.15	-
Myelin oligodendrocyte glycoprotein antibody–associated disease–related	1 (1.6)	1 (100)	30.2	1.78	0.30	0.00	-
Total	64 (100)	43 (67.2)	41.4±15.0	1.60±0.92	0.74±0.74	0.47±0.79	3.26 (1.73-6.73)

** Data are presented as mean±standard deviation or median (interquartile range)*

Table 2. Factors associated with final visual acuity improvement in multiple linear regression

Variables	β coefficient	p Value
Sex	-0.084	0.547
Age at presentation	-0.015	0.003
Presentation before March 2011	-0.738	<0.001
Time from onset to presentation	-0.029	0.087
Time from onset to treatment	0.004	0.661
Nadir visual acuity	0.532	<0.001
Visual acuity improvement on day 14	0.335	0.007
Etiology		
Idiopathic	Reference	
Post-vaccine/post-viral, acute demyelinating encephalomyelitis–related, or myelin oligodendrocyte glycoprotein antibody–associated disease–related	0.011	0.959
Multiple sclerosis–related	-0.213	0.294
Neuromyelitis optica spectrum disorder–related	0.383	0.030

eventually diagnosed with NMOSD-related ON (n=7) or acute demyelinating encephalomyelitis–related ON (n=1). All seven patients with NMOSD-related ON had nadir VA ≤20/200 at presentation (one had no light perception). After plasmapheresis, all except one patient achieved VA ≥20/30 at the final follow-up. Twelve patients were prescribed long-term maintenance immunosuppressants; they had either NMOSD-related ON (n=11) or highly steroid-responsive and steroid-dependent idiopathic ON (n=1).

Discussion

According to findings of the ONTT in 1992,[1] high-dose (1 g/day) intravenous methylprednisolone for 3 days followed by 11 days of oral prednisone resulted in better contrast sensitivity, visual field, color vision, and faster recovery; however, VA at 6 months was similar in patients with or without treatment. Oral prednisone alone did not provide additional benefit in terms of visual recovery and may even result in a higher rate of recurrent attacks. Therefore, pulse intravenous steroid treatment was considered optional, and oral prednisolone (at the ONTT dose) alone was contraindicated for patients with ON. A later study demonstrated that oral steroid treatment alone at a higher dose (ie, prednisone 1250 mg) could achieve beneficial visual outcomes, similar to the outcomes after intravenous methylprednisolone.[6] In the ONTT, 457 patients (aged 18 to 46 years) of mostly (85%) Caucasian ethnicity

were included; 92% had ocular pain and 65% exhibited retrobulbar ON without optic disc swelling. Patients with bilateral ON or evidence of systemic disease that might cause ON (other than MS) were excluded. None of the patients had anti-AQP4 antibodies, and only 1.7% had MOG-IgG antibodies.[1,3]

In Chinese patients, however, ON tends to have an atypical presentation distinct from findings in the ONTT cohort.[7,8] Ocular pain is less prevalent, as demonstrated in the present study. Although anti-AQP4 antibody seropositivity among ON cases is uncommon in Western countries, it reportedly ranges from 20% to 43.5% among Chinese patients.[4] In the present study, 25% of patients had NMOSD-related ON; they were significantly older than patients with MS-related ON. Only one patient had MOGAD-related ON. The numbers of patients with NMOSD- or MOGAD-related ON were likely underestimated because NMO and MOG serology testing only became routinely available in our center after March 2011 and April 2019, respectively.

NMOSD was considered a variant of MS but is now recognized as a distinct disease. NMOSD-related ON significantly differs from typical MS-related ON; it is characterized by a stronger predilection to women, a high incidence of bilaterality, severe visual loss, frequent involvement of the optic chiasm and a long segment of the optic nerve, and a high risk of recurrence. In the past, many cases of NMOSD-related ON were misdiagnosed as idiopathic ON. The expanding arrays of serological markers and increasing availability of anti-AQP4 antibody testing have led to improved diagnostic accuracy. Typical ON is often spontaneously resolved without treatment; however, delayed initiation of steroid treatment can be detrimental to the final visual outcome for NMOSD-related ON, which has a poor prognosis and risk of blindness.[7-11]

Similarly, MOGAD is now recognized as a distinct disorder commonly affecting children and young adults; it typically does not exhibit sex bias, unlike MS or NMOSD. Up to 50% of MOGAD-related ON is bilateral, and disc swelling is common. Patients with MOGAD-related ON are more likely to display longitudinally extensive involvement of the optic nerve and perineural enhancement on magnetic resonance imaging (MRI); they are very steroid-responsive and sometimes steroid-dependent, requiring slow tapering of oral steroid treatment and even long-term immunosuppressant therapy, especially in recurrent cases. MOGAD can be monophasic or relapsing, but there is no progressive phase. Although initial visual loss can be severe, similar to NMOSD-related ON, final visual outcomes generally are better.[9-14]

Non-infectious differential diagnoses of acute ON include demyelinating disease (with or without concurrent MS), NMOSD, and MOGAD. Historically, typical ON was diagnosed via clinical examination; MRI of the brain was performed to predict future risk of MS development. Considering the improved understanding of the radiological features of NMOSD- and MOGAD-related ON, MRI can now be used to differentiate etiologies of ON. Since the discovery of anti-AQP4 and MOG-IgG antibodies, tests of these antibodies have been recommended to guide treatment for all patients with acute ON. Cell-based assays are the preferred serological tests for anti-AQP4 and MOG-IgG antibodies. However, the turnaround time for these tests can take 1 to 2 weeks.[9,15-17] In the acute setting, where the diagnosis of ON is certain but the underlying etiology is unknown, clinicians must decide whether to initiate steroid treatment. Steroid was considered optional in ONTT, but it is important to note that almost all cases in the ONTT were idiopathic or MS-related and thus application of the ONTT findings to Chinese population is limited.

In our hospital, we routinely offer pulse intravenous steroid treatment followed by an oral taper regimen for patients with ON. We advocate early steroid treatment for Chinese patients, considering the different disease spectrum compared with Caucasians. In the present study, NMOSD-related ON was significantly associated with greater final VA improvement. This highlights its unique features: high responsiveness to and dependence on steroid treatment and presentation with more severe visual loss. VA improvement on day 14 was an important predictor of final VA improvement. In clinical settings, VA improvement on day 14 can help clinicians determine the speed of oral steroid tapering and communicate with patients to adjust expectations for visual recovery. Additionally, we identified age as an independent predictor of smaller final VA improvement, consistent with previous findings.[18] We speculate that older people have less neuroplasticity and are more likely to have vasculopathy that can predispose them to additional ischemic injury during episodes of optic nerve inflammation.

Serologic testing for anti-AQP4 antibodies was introduced to our laboratory in March 2011; it was initially performed in patients with high clinical suspicion of NMOSD but quickly became free of charge for any patient with suspected ON and is now the standard practice. Although the turnaround time is 1 to 2 weeks, anti-AQP4 antibody testing enables earlier and more accurate diagnosis of NMOSD, as well as earlier initiation of steroid and immunosuppressant treatments for NMOSD. In patients with refractory ON, plasmapheresis is effective for NMOSD- or MOGAD-related ON and can be offered more promptly when the diagnosis is made.[9,19]

All patients with NMOSD-related ON or severe or recurrent attacks of MOGAD-related ON require maintenance immunosuppressants such as azathioprine, mycophenolate mofetil, and rituximab. For the management of NMOSD, newer biologics such as eculizumab (complement activation inhibitor), tocilizumab, and satralizumab (anti-interleukin-6 antibody) have demonstrated superior efficacy. Thus, patients with NMOSD and MOGAD should be co-managed by ophthalmologists, neurologists, and rheumatologists.[20-24]

Limitations of the present study include its retrospective nature and evaluation of visual function with VA alone;

data regarding color vision, visual field, contrast sensitivity, or anatomical evaluations (eg, retinal nerve fiber layer thickness on optical coherence tomography) were either incomplete or unavailable. The proportions of patients with NMOSD-related ON and MOGAD-related ON were likely underestimated because patients who presented before the introduction of anti-AQP4 or MOG-Ig serology tests were likely to have been misdiagnosed as having idiopathic ON.

Conclusion

Because treatment outcomes differ among MS-, NMOSD-, and MOGAD-related ON, ophthalmologists should be aware of new biomarkers for ON; NMO and MOG serology testing should be conducted for all patients with ON, in addition to MRI of the brain and orbit. In the Chinese population, a considerable proportion of patients with acute ON exhibit atypical disease characteristics; therefore, pulse intravenous steroid treatment should be considered necessary (rather than optional), even before serology results are available. Over the years, VA improvement is likely the result of enhanced investigations and more aggressive treatment of NMOSD-related ON.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: 621-KCKE). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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