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Clinical trial

The clinical spectrum and prognosis of idiopathic acute optic neuritis: A longitudinal study in Southern Finland

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ABSTRACT

Background: To analyse in a population-based setting the clinical features, prognostic factors, and seasonality of patients diagnosed with acute idiopathic optic neuritis (ON).
Methods: Retrospective analysis of ophthalmological records, laboratory parameters, and magnetic resonance imaging (MRI) of patients with symptoms suggestive of ON referred to the Helsinki University Hospital (serving a population of 1.53 million in Southern Finland) were analysed between May 1, 2008 and April 14, 2012.
Results: Of the 291 patients with suspected ON, 184 (63%) were diagnosed with ON (mean age 34 years, 76% females). Intravenous methylprednisolone treatment was administered in 131 (71%) patients. First ON was diagnosed in 123 patients (67%), 55 (30%) had a previous diagnosis of multiple sclerosis (MS) and two patients with their first ON were diagnosed with neuromyelitis optica. Evolution of best corrected visual acuity (BCVA) was analysed in 132 (72%) patients, who were reviewed median of 38 days after onset. Median and mean BCVAs in these reviewed patients were 0.4 and 0.2 at the time of diagnosis and 1.0 and 0.5 at the time of the review. Recovery was relatively good in the majority of patients; 82% (n = 108) had reached BCVA of ≥0.5 and 70% (n = 92) and BCVA of ≥0.8 at the time of the review, while thirteen (10%) had poor prognosis, BCVA ≤0.1 at review. Accessory clinical features included optic disc swelling (21%), colour vision impairment (75%), and pain with eye movements (65%). Relative afferent pupillary defect was abnormal in 76% of the patients with their first ON. Baseline visual acuity was most strongly associated with visual outcome at review ($P < 0.001$, linear regression). Optic disc swelling and the presence of lesions in the optic nerve on MRI had a more modest association with poorer recovery ($P = 0.033$ and $P = 0.049$, respectively), while age, sex, previous history of ON, and previous diagnosis of multiple sclerosis were not associated with outcome at review. Incidence of ON showed a clear seasonal pattern; there were two times more cases in April to June versus October to December ($P = 0.03$), confirming previous results from Sweden.
Conclusions: Our data suggest that besides baseline visual acuity, optic disc swelling and lesions in the optic nerve on MRI are associated with poorer prognosis. As in previous studies, we observed that diagnostics of ON is difficult, accessory clinical findings such as pain and RAPD are not always present. Although the diagnosis of ON is clinical, the role of MRI should be considered in differential diagnostics and in defining potential prognostic markers.

1. Introduction

Optic neuritis (ON) is a demyelinating disease that causes inflammation of the optic nerve often leading to subacute vision loss. ON mostly affects young adults and more often females. The diagnosis of ON is essentially clinical; no universal diagnostic criteria are available (Hickman et al., 2002). It has become increasingly evident that a substantial portion of patients with suspected ON do not have genuine ON (Siuko et al., 2018, Stunkel et al., 2018). Accordingly, efforts should be made to improve diagnostic accuracy. The most common symptom of ON is decreased visual acuity. Other common symptoms are impaired colour vision and pain upon eye movement. Patients typically have abnormal visual-evoked potentials (VEP) and central visual field defects. Relative afferent pupillary defect (RAPD) is present unless the optic nerve involvement is bilateral and symmetric. The optic disc may swell when the inflammation occurs in its immediate vicinity (a

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condition called papillitis), but often it remains normal in appearance. No specific treatment is known for ON. According to the Optic Neuritis Treatment Trial (ONTT), intravenous high-dose corticosteroids may hasten visual recovery, but they do not improve the 6-month and 1-year outcome of visual acuity compared to placebo (Beck et al., 1992).

ON is the presenting symptom of relapsing multiple sclerosis (MS) in about one quarter of cases and eventually occurs in about two thirds of patients. ON is also a common initial symptom and one of the main diagnostic criteria of neuromyelitis optica (NMO, or Devic's disease), another demyelinating disease characterized by spinal symptoms from longitudinally extensive myelitis. Aquaporin-4 (AQP4) antibodies are a supporting diagnostic criterion of NMO (Wingerchuk et al., 2006, Weinshenker et al., 2006, McKeon et al., 2009). Nowadays the diagnostic criteria of NMO have evolved significantly and this syndrome is renamed as neuromyelitis optica spectrum disorders (Wingerchuk et al., 2015). ON in NMO is typically severe and often bilateral. In AQP4 antibody-positive NMO cases, poor prognosis is associated with young age and Afro-Caribbean ethnicity in a UK cohort (Kitley et al., 2012). However, in the more common forms of ON there are minimal data on prognostic factors.

Here, we critically evaluated the baseline findings and prognosis in follow up of 184 patients with acute or subacute visual impairment from ON. In addition to the clinical visits, the evaluation was based on magnetic resonance imaging (MRI) and laboratory tests.

2. Materials and methods

All patients referred to the Department of Ophthalmology in the Helsinki University Hospital, Finland, between May 1, 2008 and April 14, 2012 (a period of 47.5 months) with symptoms suggestive of acute or subacute ON were eligible for inclusion. Finland has a national health insurance scheme that covers all residents. Therefore, selection bias is minimal and the hospital receives virtually all patients with an acute ON living in its catchment area, the Hospital District of Helsinki and Uusimaa in Southern Finland. This region had a mean population of 1.53 million during our study period (28% of the population of Finland, 5.4 million in 2011). Therefore, our sample is essentially population-based in the geographic catchment area, without administrative selection criteria.

The diagnosis of ON is clinical and no universal diagnostic criteria are available. We adhered to some of the most common criteria, namely a combination of acute or subacute loss of vision associated with RAPD, pain upon eye movements, and some degree of acquired color vision deficiency. At the time of our patient recruitment, 2008-2012, we used the diagnostic criteria of NMO from 2006 (Wingerchuk et al., 2006).

Biomicroscopic examination of the fundus was performed in all patients. Visual fields, VEPs, and optical coherence tomography were performed in some patients as necessary to ascertain the diagnosis of ON (Fard et al., 2018). Best corrected visual acuity (BCVA) was measured with a Snellen chart. For statistical analysis, visual acuity was converted to logMAR scale. RAPD was graded positive, negative, or unknown. Eye movements were coded painful, not painful, or unknown. Colour vision was measured by the Ishihara 24 plates test. Colour vision was considered impaired if more than one error occurred (Ishihara Instructions of The Series of Plates Designed as a Test for Colour Deficiency Shinobu Ishihara M.D., Dr. Med. Sc. Professor Emeritus of the University of Tokyo). The optic disc was coded as swollen or not swollen. Most of the ON patients were first seen and reviewed by residents in the emergency department. When the diagnosis was equivocal, a senior consultant also examined the patient. The first review of all ON patients in our praxis has been approximately 1 month after the onset. Prognosis was analysed by comparing median and mean BCVAs at the time of the diagnosis and at least 30 days later. The cut-off time of 30 days was chosen since in the ONTT a significant proportion of the recovery was noticed already one month after the onset (Beck et al., 1992, Beck et al., 1994).

Table 1
Factors influencing the severity and recovery of the optic neuritis (ON) among patients reviewed after 30 days or more, $n = 132$.

	Visual acuity* at onset (range)	Visual acuity* at review (range)
All	0.4/0.2 (CF-1.0)	1.0/0.5 (CF-1.0)
Sex	$p = 0.54^{\dagger}$	$p = 0.62^{\dagger}$
Female ($n = 101$)	0.4/0.2 (CF-1.0)	0.8/0.5 (CF-1.0)
Male ($n = 31$)	0.4/0.2 (CF-1.0)	1.0/0.5 (0.1-1.0)
Age	$p = 0.12^{\ddagger}$	$p = 0.89^{\ddagger}$
Age >45 ($n = 22$)	0.4/0.3 (CF-0.9)	1.0/0.6 (CF-1.0)
Age 25–45 ($n = 88$)	0.4/0.2 (CF-1.0)	1.0/0.6 (CF-1.0)
Age <25 ($n = 22$)	0.2/0.1 (CF-0.8)	1.0/0.4 (CF-1.0)
Setting	$p = 0.20^{\dagger}$	$p = 0.23^{\dagger}$
First ON ($n = 87$)	0.4/0.2 (CF-1.0)	1.0/0.5 (CF-1.0)
Recurrent ON ($n = 45$)	0.4/0.3 (CF-1.0)	1.0/0.5 (CF-1.0)
Diagnosis of MS	$p = 0.71^{\dagger}$	$p = 0.28^{\dagger}$
Yes ($n = 55$)	0.4/0.3 (CF-0.8)	1.0/0.5 (CF-1.0)
No ($n = 77$)	0.4/0.2 (CF-1.0)	1.0/0.5 (CF-1.0)
Site	$p = 0.85^{\dagger}$	$p = 0.033^{\dagger}$
Optic disc swelling ($n = 28$)	0.4/0.2 (CF-1.0)	0.9/0.5 (CF-1.0)
No optic disc swelling ($n = 104$)	0.4/0.2 (CF-1.0)	1.0/0.6 (CF-1.0)
All MRI screened patients, $n = 98$	$p = 0.051^{\dagger}$	$p = 0.049^{\dagger}$
Lesions in optic nerve ($n = 70$)	0.2/0.1 (CF-1.0)	0.9/0.5 (CF-1.0)
No lesions in optic nerve ($n = 28$)	0.4/0.3 (CF-1.0)	1.0/0.6 (CF-1.0)
MRI screened first ON patients, $n = 77$	$p = 0.17^{\dagger}$	$p = 0.081^{\dagger}$
Lesions in optic nerve ($n = 57$)	0.3/0.1 (CF-1.0)	0.9/0.5 (CF-1.0)
No lesions in optic nerve ($n = 20$)	0.4/0.3 (CF-1.0)	1.0/0.6 (CF-1.0)

CF = counting fingers; MRI = magnetic resonance imaging of brain and orbits; MS = multiple sclerosis. Visual acuity at review was worse among patients with swelling in optic nerve ($p = 0.033$) and among patients with MRI lesions in optic nerve ($p = 0.049$).

* Median and mean visual acuity.
† Mann–Whitney U test.
‡ Jonckheere Terpstra test for ordered alternatives.

MRI of the brain and orbits was performed within 24 hours after hospital admission, either with a Siemens Avanto 1.5T (Siemens AG, Erlangen, Germany), Philips Achieva 3T (Philips Healthcare, Eindhoven, The Netherlands), or Siemens Verio 3T (from 2011). The MRI included T2, T2 flair, and diffusion-weighted and T1 sequences with gadolinium enhancement. MRI was not performed in 49 patients in acute phase for the following reasons: in 41 patients MRI had been performed recently as a part of MS patient follow-up, four patients were referred immediately to a neurologist before MRI screening, and five patients had other reasons (e.g., claustrophobia). A spinal MRI was obtained in all patients with spinal cord symptoms or positive or borderline AQP4 index. Laboratory parameters, except AQP4 antibodies, were analysed in the clinical laboratory of the Helsinki University Hospital. AQP4 autoantibodies were measured by radioimmunoprecipitation in the laboratory of Prof. H.P. Seelig, Karlsruhe, Germany.

Statistical analysis was performed using SPSS v.22 (Chicago, IL, SPSS Inc.). Data were tested for normality using the Jonckheere Terpstra test for ordered alternatives and Mann–Whitney U test for differences between two independent groups. Categorical variables were compared using Fisher's exact test. Stata Statistical Software Release 15 (College Station, TX, StataCorp LLC) was used to perform the Walter–Elwood test (Walter, 1977) for monthly distribution of patients and the linear regression of the development of visual acuities. Statistical significance was assumed at the 5% level.

This study was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (Dnro 83/13/03/01/2013).

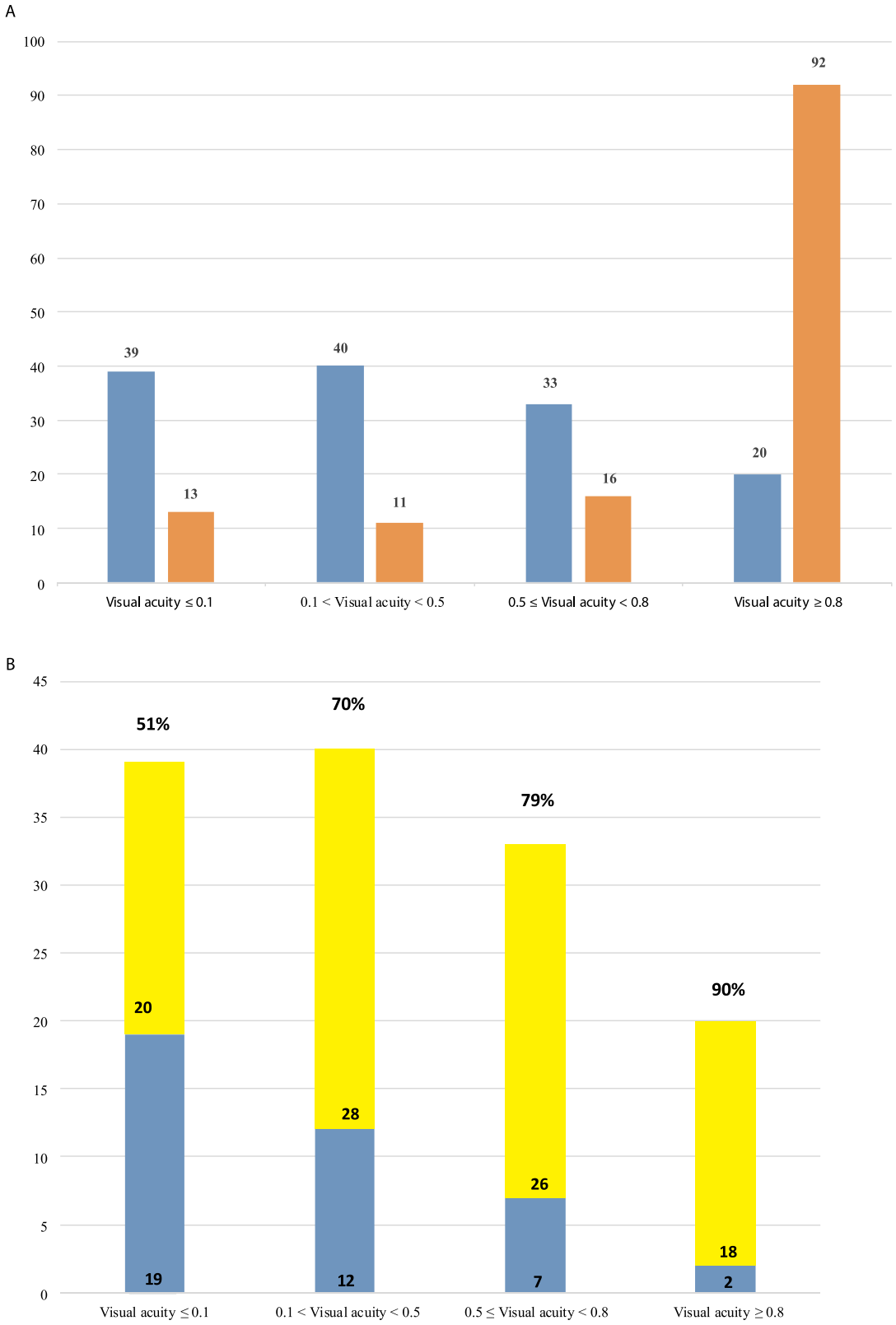

Fig. 1. (a) Visual acuity of patients with optic neuritis at onset and at the time of the review (n = 132). (b) Percentage of patients reaching visual acuity ≥0.8 at review (n = 132). Number of patients with optic neuritis based on visual acuity (VA) at onset and at the time of the review in four subgroups (VA ≤ 0.1, 0.1 < VA < 0.5, 0.5 ≤ VA < 0.8, VA ≥ 0.8). Review time of all patients was ≥30 days from onset. Blue column = number of patients at onset. Orange column = number of patients at review. Yellow column = number of patients at review with VA ≥ 0.8. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

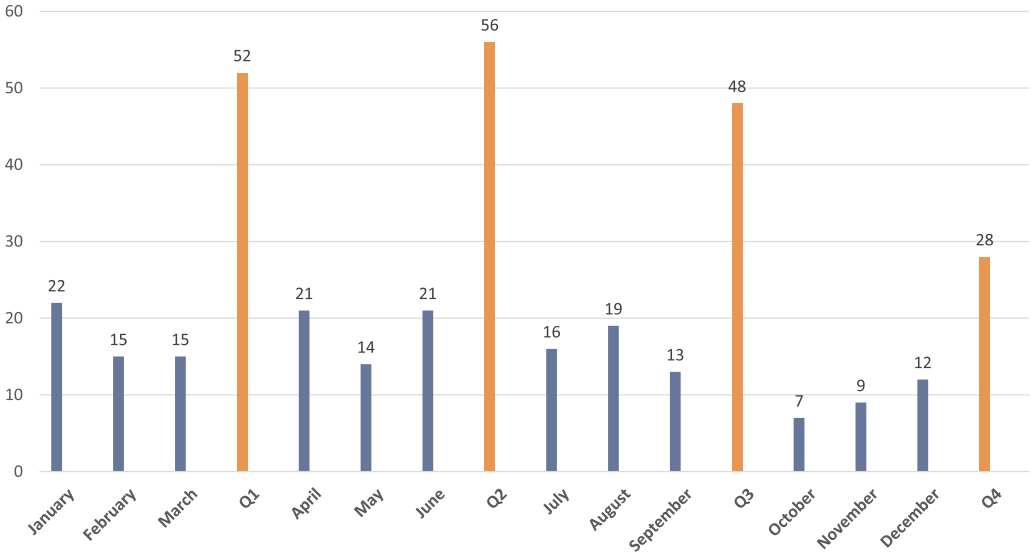

Fig. 2. Seasonal variation of the incidence of optic neuritis. Both monthly (blue) and quarterly (orange) incidence figures are shown. Q1 = January–March, Q2 = April–June, Q3 = July–September, Q4 = October–December. There was a significant difference in monthly distribution of patients with ON ($p = 0.026$) by Walter–Elwood test (Walter, 1977). The quarterly incidence of optic neuritis was highest in Q2 and lowest in Q4, and the Q2 vs. Q4 comparison demonstrated an odds ratio of 2.0 for Q2 (95% CI 1.09–3.68, $p = 0.03$, Fisher's exact test). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Study population

During the study period, 291 patients with a condition suggestive of ON were examined; 184 (63%) were diagnosed with ON and 107 (37%) with another condition. These other conditions have been reported previously (Siuko et al., 2018).

Mean age was 34 years (range 15–61 years) and 76% were female. First ON was observed in 123 (67%) patients. Fifty-five patients (30%) had a previous diagnosis of MS; two patients with their first ON were diagnosed with NMO. Intravenous methylprednisolone treatment was administered in 131 (71%) of the 184 verified ON patients. The most common reasons for not offering this treatment to an ON patient were close to normal visual acuity and treatment refusal by the patient.

RAPD was tested in 121 patients with their first ON and was positive in 92 (76%). The interquartile range of BCVA among RAPD-negative patients was 0.1–0.6. Three patients (1.6%) had bilateral ON; two of them were diagnosed with MS and one with NMO. Of the 61 patients with a previous history of unilateral ON, recurrent ON occurred in the same eye in 27 (44%) and in the other eye in 15 (25%) patients. There was insufficient evidence to conclude that this distribution deviated from chance ($P = 0.088$, binominal test). Demographics and clinical characteristics are shown in Table 1.

3.2. Visual acuity

The median and mean BCVAs at the time of diagnosis of ON were 0.2 and 0.1 (range 0–1.0). Evolution of BCVA was analysed in 132 (72%) patients, who were reviewed ≥30 days after onset (median 38 days). Median and mean BCVAs in these 132 reviewed patients were 0.4 and 0.2 at the time of diagnosis and 1.0 and 0.5 at the time of the review. Recovery was relatively good in the majority of patients; 82% ($n = 108$) and 70% ($n = 92$) had reached BCVA of ≥0.5 and ≥0.8, respectively, at the time of the review, while thirteen (10%) had poor prognosis (BCVA ≤ 0.1) at review (Fig. 1A). Fig. 1B shows the percentage of patients with good prognosis (BCVA of ≥0.8) according to baseline visual acuity and demonstrates that the baseline visual acuity might be associated with outcome ($P = 0.083$, non-parametric test for trend). An alternative analysis with finer resolution of BCVA using linear regression supported this hypothesis between baseline visual acuity and visual acuity at review ($P < 0.001$).

In addition to baseline BCVA, we analysed which factors might modulate the recovery of ON. Among the 132 patients, visual acuity at onset and at review was not significantly associated with sex, age, first or recurrent ON or diagnosis of MS (Table 1). However, we found that visual acuity at review was poorer among patients with swelling in the optic nerve ($P = 0.033$, Mann–Whitney U-test) and among patients with MRI lesions in the optic nerve ($P = 0.049$, Mann–Whitney U test) (Table 1). We also compared the demographic and clinical characteristics of the patients with poor prognosis (BCVA ≤ 0.1 at review) to those with good prognosis (BCVA ≥ 0.8 at review) but did not find major differences between these two groups (Supplementary Table 1).

Fifteen laboratory parameters were analysed from blood as part of ongoing clinical trials: erythrocyte sedimentation rate, C-reactive protein, full blood count (erythrocytes, leukocytes, platelets), calcium, sodium, potassium, albumin, creatinine, alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase, glucose, thyroid stimulating hormone, and *Borrelia afzelii, Borrelia burgdorferi* and AQP4 antibodies. Myelin oligodendrocyte glycoprotein antibodies were not screened. A pregnancy test was also performed for women (two positive cases). We analysed the association of baseline abnormalities of these laboratory parameters with baseline BCVA and BCVA at review but did not find any significant associations. Eighteen (10%) patients had a positive *B. burgdorferi* IgG antibody test, similar to the seroprevalence in the Southern Finland general population (Oksi et al., 2013); there was no association between seropositivity and BCVA at baseline or at review (data not shown). None of the seropositive patients were diagnosed with acute Lyme disease, but one patient was treated for Lyme disease in 2006. A positive AQP4 antibody index was observed in three patients (one with NMO, two with MS); details of these patients have been previously described (Siuko et al., 2014). The mean AQP4 antibody index was not associated with BCVA at baseline or at review. The mean AQP4 antibody index and pathological AQP4 indexes (Siuko et al., 2014) were also compared in the patients with poor (BCVA ≤ 0.1 at review) and good prognosis (BCVA ≥ 0.8 at review) but there were no significant differences between these two groups (Supplementary Table 1).

3.3. Seasonality

The incidence of ON was analysed by month and by season (Q1 = January–March, Q2 = April–June, Q3 = July–September, Q4 = October–December). The quarterly incidence of ON was highest in Q2 and lowest in Q4. The Q2 versus Q4 comparison had an odds ratio of 2.0 for Q2 (95% confidence interval 1.09–3.68, $P = 0.030$, Fisher's exact test), which is similar to the data from Sweden (Jin et al., 2000) Using the Walter–Elwood test (Walter, 1977), we observed a significant

Table 2
Comparison of demographical and clinical characteristics of optic neuritis patients from the present and previous studies.

Region and study period	Number of patients	Mean age at time of the diagnosis	F/M ratio	Ocular pain/pain with eye movements (%)	Optic disc swelling (%)	Diagnosis of MS at onset (%)	Diagnosis of NMO at onset (%)
Finland 2008–2012*	184	34	3.2	64	21	30	1
Denmark 2014–2016 (Soelberg et al., 2017)	51	38 (median)	2.2	65	n.a.	n.a.†	n.a.†
China 2002–2005 (Zhang et al., 2017)	98	26	1.2	43	40	8	4
Singapore 2002–2004 (Lim et al., 2008)	55	n.a.	3.2	71	60	26	n.a.
Japan 1991–1996 (Wakakura et al., 1999)	70	36	2.2	43	50	6	n.a
Sweden 1990–1995 (Jin et al., 1998)	150	32	4.1	n.a.	n.a.	n.a.†	n.a.†
USA 1988–1991 (Optic Neuritis Study Group., 1991)	448	32	3.4	92	35	13	n.a.

F/M = female/male, MS = multiple sclerosis, NMO = neuromyelitis optica, n.a. = not available.
* Present study.
† Patients with MS and NMO were excluded from the study.

difference in the monthly distribution of ON patients (P = 0.026) (Fig. 2).

4. Discussion

After ONTT this study is the second largest population-based analysis of ON patients. Table 2 outlines our data in relation to other ON cohorts. In our cohort of ON patients, the female:male ratio (3:2) is slightly higher from the current ratio in patients with MS (2.5:2 among 2631 MS patients, data from the Finnish MS register) in the same catchment area. In previous ON studies from elsewhere the female:male ratio has varied considerably, from as low as 1.2 in China (Zhang et al., 2007) to 4.1 in Sweden (Jin et al., 1998) (Table 2). In our cohort, bilateral ON (1.6%) and NMO (1%) were rare. In New York, USA, 6.4% of the ON patients had bilateral disease (de la Cruz & Kupersmith, 2006) and in China the proportion of bilateral cases was exceptionally high (32.7%) (Zhang et al., 2007), which is probably attributable to the higher relative frequency of NMO, in which bilateral ON is common. Of the population in our catchment area during 2008 to 2012, 2% have Asian background (Statistics Finland), but all ON patients in this study were Caucasians. Almost a third (30%) of the patients had a previous diagnosis of MS which, however, did not have significant effect on the initial severity or short-term recovery of ON. The high number of patients with MS in our study population is consistent with the high incidence and prevalence of MS in Finland (Sumelahti et al., 2000, 2001; Krökki et al. 2011).

Patients with recurrent ON had slightly (but not statistically significantly) better initial visual acuities than patients with their first ON. This counterintuitive finding might be due to increased awareness of ON symptoms and therefore these patients may have consulted ophthalmologists at an earlier phase. Visual acuity recovered remarkably similarly in most patient subgroups, indicating that age, sex, and previous ON or diagnosis of MS did not have any significant effect on recovery of visual acuity. Previously, in a smaller study it has been reported that males (n = 8) have a poorer 3 month recovery than females (n = 42) (Costello et al 2015). Baseline visual acuity had a clear effect on outcome (Fig. 1) as observed previously (Zhang et al. 2007). The observation of significantly lower recovery of vision in patients with optic disc swelling and MRI lesions in the optic nerve indicates a heavier lesion load in the visual system of these patients. More work is needed to evaluate the feasibility of lesion load as a prognostic marker.

As in previous studies, we observed that diagnostics of ON are difficult since in addition to decreased visual acuity, supporting clinical findings are often absent. Pain and RAPD are considered hallmarks of acute ON. It is of note that 24% of the patients did not have RAPD, which we assume is because the ON was mild or in an early phase such that RAPD could have been missed. Furthermore, pain was not reported in 36% of patients, indicating that ON without pain is relatively common as also previously observed. The diagnosis of ON is clinical but since the clinical findings of an ON patient may be subtle, the role of ancillary testing, like MRI, plays a role in supporting and differentiating the diagnosis (Chan, 2012; Kupersmith et al., 2002; Fard et al., 2018).

The exacerbation and development of autoimmune diseases are suggested to have seasonality (Watad et al., 2017) and even the month of birth is considered a risk factor for future development of autoimmune diseases (Templer et al., 1992; Willer et al., 2005; Bayes et al., 2010; Saastamoinen et al., 2012). Two suspected factors are low vitamin D and melatonin levels. Both levels are at the lowest during spring time, which is the same period when the highest incidence of MS is recorded (Schapira, 1959; Spelman et al., 2014). Many other autoimmune diseases are also reported to be associated with seasonal factors, such as systemic lupus erythematosus, type 1 diabetes mellitus, inflammatory bowel diseases, rheumatoid arthritis, autoimmune liver diseases, autoimmune thyroid disease, celiac disease, Sjögren's syndrome, systemic sclerosis, and psoriasis. Our findings of the seasonality of ON are consistent with previous ON and MS studies, which

documented the low incidence of ON during the last quarter of the year (Templer et al., 1992; Jin et al., 1999; Willer et al., 2005)

There are limitations of this study that affect the generalization of the results. First, the study population was from Southern Finland and all patients were Caucasians. Thus, these results do not necessarily apply to other ethnic groups. Second, not all patients necessarily seek medical attention during acute ON; these include very mild cases and socially excluded subjects and this may influence case ascertainment. Third, with regards to prognosis, the results may be affected by varying follow-up times among patients. This time-window does not allow follow-up of the complete recovery of BCVA, which may take several months (Costello et al., 2015). Fourth, not all examinations (for practical reasons) were performed on every patient, which slightly reduces the amount of available data and power of the study. A larger scale study should be performed to identify more subtle associations with severity and prognosis.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.08.007.

References

Bayes, H.K., Weir, C.J., O'Leary, C., 2010. Timing of birth and risk of multiple sclerosis in the Scottish population. Eur. Neurol. 63, 36–40. https://doi.org/10.1159/000268163.

Beck, R.W., Cleary, P.A., Anderson Jr, M.M., Keltner, J.L., Shults, W.T., et al., 1992. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N. Engl. J. Med. 326, 581–588. https://doi.org/10.1056/NEJM199202273260901.

Beck, R.W., Cleary, P.A., Backlund, J.C., 1994. The course of visual recovery after optic neuritis. Experience of the Optic Neuritis Treatment Trial. Ophthalmol 101, 1771–1778. https://doi.org/10.1016/S0161-6420(94)31103-1.

Chan, J.W., 2012. Early diagnosis, monitoring, and treatment of optic neuritis. Neurologist 18, 23–31. https://doi.org/10.1097/NRL.0b013e31823d7acd.

Costello, F., Y2, Pan, Yeh, E.A., Hodge, W., Burton, J.M., Kardon, R, 2015. The temporal evolution of structural and functional measures after acute optic neuritis. J. Neurol. Neurosurg. Psyc. 86, 1369–1373. http://dx.doi.org/10.1136/jnnp-2014-309704.

de la Cruz, J., Kupersmith, M.J., 2006. Clinical profile of simultaneous bilateral optic neuritis in adults. Br. J. Ophthalmol. 90, 551–554. https://doi.org/10.1136/bjo.2005.085399.

Fard, M.A., Jalili, J., Sahraiyan, A., Khojasteh, H., Hejazi, M., Ritch, R., Subramanian, P.S., 2018. Optical coherence tomography angiography in optic disc swelling. Am. J. Ophthalmol. 191, 116–123. https://doi.org/10.1016/j.ajo.2018.04.017.

Hickman, S.J., Dalton, C.M., Miller, D.H., Plant, G.T., 2002. Management of acute optic neuritis. Lancet 360, 1953–1962. https://doi.org/10.1016/S0140-6736(02)11919-2.

Jin, Y., de Pedro-Cuesta, J., Soderstrom, M., Stawiarz, L., Link, H., 2000. Seasonal patterns in optic neuritis and multiple sclerosis: a meta-analysis. J. Neurol. Sci. 181, 56–64. https://doi.org/10.1016/S0022-510X(00)00408-1.

Jin, Y.P., de Pedro-Cuesta, J., Soderstrom, M., Stawiarz, L., Link, H., 1998. Incidence of optic neuritis in Stockholm, Sweden 1990-1995: I. Age, sex, birth and ethnic-group related patterns. J. Neurol. Sci. 159, 107–114. https://doi.org/10.1016/S0022-510X(98)00141-5.

Jin, Y.P., de Pedro-Cuesta, J., Soderstrom, M., Link, H., 1999. Incidence of optic neuritis in Stockholm, Sweden, 1990-1995: II. Time and space patterns. Arch. Neurol. 56, 975–980. https://doi.org/10.1001/archneur.56.8.975.

Kitley, J., Leite, M.I., Nakashima, I., Waters, P., McNeillis, B., Brown, R., et al., 2012. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain 135, 1834–1849. https://doi.org/10.1093/brain/aws109.

Krökki, O., Bloigu, R., Reunanen, M., Remes, A.M., 2011. Increasing incidence of multiple sclerosis in women in Northern Finland. Mult. Scler. 17, 133–138. https://doi.org/10.1093/brain/aws109.

Kupersmith, M.J., Alban, T., Zeiffer, B., Lefton, D., 2002. Contrast-enhanced MRI in acute optic neuritis: relationship to visual performance. Brain 125, 812–822. https://doi.org/10.1093/brain/awf087.

Lim, S.A., Goh, K.Y., Tow, S., Fu, E., Wong, T.Y., Seah, A., Tan, C., Cullen, J.F., 2008. Optic neuritis in Singapore. Singapore Med. J. 49, 667–671.

McKeon, A., Fryer, J.P., Apiwattanakul, M., Lennon, V.A., Hinson, S.R., Kryzer, et al., 2009. Diagnosis of neuromyelitis spectrum disorders: comparative sensitivities and specificities of immunohistochemical and immunoprecipitation assays. Arch. Neurol. 66, 1134–1138. https://doi.org/10.1001/archneurol.2009.178.

Oksi, J, Seppälä, J, Hytönen, J, 2013. Borrelia Burgdorfer and Lyme's borreliosis. Infektiosairaudet – Mikrobiologia, immunologia ja infektiosairaude. Duodecim, , Helsinki, Finland (in Finnish).

Optic Neuritis Study Group, 1991. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Arch. Ophthalmol. 109, 1673–1678. https://doi.org/10.1001/archopht.1991.01080120057025.

Saastamoinen, K.P., Auvinen, M.K., Tienari, P.J., 2012. Month of birth is associated with multiple sclerosis but not with HLA-DR15 in Finland. Mult. Scler. 18, 563–568. https://doi.org/10.1177/1352458511426814.

Schapira, K., 1959. The seasonal incidence of onset and exacerbations in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 22, 285–286. https://doi.org/10.1136/jnnp.22.4.285.

Siuko, M., Tienari, P.J., Saastamoinen, K.P., Atula, S., Miettinen, A., Kivela, T., Setala, K., 2014. Neuromyelitis optica and aquaporin-4 (AQP4) autoantibodies in consecutive optic neuritis patients in Southern Finland. Acta Ophthalmol 92, 387–391. https://doi.org/10.1111/aos.12187.

Siuko, M., Kivela, T.T., Setala, K., Tienari, P.J., 2018. Incidence and mimickers of acute idiopathic optic neuritis: analysis of 291 consecutive patients from Southern Finland. Ophthal. Epidemiol. 25, 386–391. https://doi.org/10.1080/09286586.2018.1500614.

Soelberg, K., Jarius, S., Skejoe, H., Engberg, H., Mehlsen, J.J., Nilsson, A.C., et al., 2017. A population-based prospective study of optic neuritis. Mult. Scler. 23, 1893–1901.

Spelman, T., Gray, O., Trojano, M., Petersen, T., Izquierdo, G., Lugaresi, A., et al., 2014. Seasonal variation of relapse rate in multiple sclerosis is latitude dependent. Ann. Neurol. 76, 880–890. https://doi.org/10.1177/1352458517734070.

Stunkel, L., Kung, N.H., Wilson, B., McClelland, C.M., Van Stavern, G.P., 2018. Incidence and causes of overdiagnosis of optic neuritis. JAMA Ophthalmol. 136, 76–81. https://doi.org/10.1001/jamaophthalmol.2017.5470.

Sumelahti, M.L., Tienari, P.J., Wikstrom, J., Palo, J., Hakama, M., 2000. Regional and temporal variation in the incidence of multiple sclerosis in Finland 1979-1993. Neuroepidemiology 19, 67–75. https://doi.org/10.1159/000026241.

Sumelahti, M.L., Tienari, P.J., Wikstrom, J., Palo, J., Hakama, M., 2001. Increasing prevalence of multiple sclerosis in Finland. Acta Neurol. Scand. 103, 153–158. https://doi.org/10.1136/jnnp.74.1.25.

Templer, D.I., Trent, N.H., Spencer, D.A., Trent, A., Corgiat, M.D., Mortensen, P.B., Gorton, M., 1992. Season of birth in multiple sclerosis. Acta Neurol. Scand. 85, 107–109. https://doi.org/10.1111/j.1600-0404.1992.tb04007.x.

Wakakura, M., Minei-Higa, R., Oono, S., Matsui, Y., Tabuchi, A., Kani, K., et al., 1999. Baseline features of idiopathic optic neuritis as determined by a multicenter treatment trial in Japan. Optic Neuritis Treatment Trial Multicenter Cooperative Research Group (ONMRG). Jpn. J. Ophthalmol. 43, 127–132. https://doi.org/10.1016/S0021-5155(98)00072-0.

Walter, S.D., 1977. The power of a test for seasonality. Br. J. Prev. Soc. Med. 31, 137–140. https://doi.org/10.1136/jech.31.2.137.

Watad, A., Azrielant, S., Bragazzi, N.L., Sharif, K., David, P., Katz, I., et al., 2017. Seasonality and autoimmune diseases: the contribution of the four seasons to the mosaic of autoimmunity. J. Autoimmun. 82, 13–30. https://doi.org/10.1016/j.jaut.2017.06.001.

Weinshenker, B.G., Wingerchuk, D.M., Pittock, S.J., Lucchinetti, C.F., Lennon, V.A., 2006. NMO-IgG: a specific biomarker for neuromyelitis optica. Dis. Markers 22, 197–206. https://doi.org/10.1155/2006/586306.

Willer, C.J., Dyment, D.A., Sadovnick, A.D., Rothwell, P.M., Murray, T.J., Ebers, G.C., Canadian Collaborative Study Group, 2005. Timing of birth and risk of multiple sclerosis: population based study. BMJ 330, 120. https://doi.org/10.1136/bmj.38301.686030.63.

Wingerchuk, D.M., Lennon, V.A., Pittock, S.J., Lucchinetti, C.F., Weinshenker, B.G., 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology 66, 1485–1489. https://doi.org/10.1212/01.wnl.0000216139.44259.74.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., International Panel for NMO Diagnosis, 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85, 177–189. https://doi.org/10.1212/WNL.0000000000001729.

Zhang, X., Wang, W., Wang, Q., Cui, S., Wei, W., 2007. Clinical features of optic neuritis in China. Neuro-Ophthalmology 31, 133–136. https://doi.org/10.1080/01658100701647506.