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ORIGINAL COMMUNICATION

Is the incidence of optic neuritis rising? Evidence from an epidemiological study in Barcelona (Spain), 2008–2012

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Abstract It is currently believed that the incidence rate of optic neuritis (ON) ranges between 0.56 and 5.1 cases per 100,000 person-years. However, since these figures were generated, they have not been updated and there are suggestions that the incidence of ON is on the rise. When designing new therapies and clinical trials for ON, and to improve the management this disease, it is important to have accurate epidemiological data. Thus, we set out to obtain the prevalence and incidence rates of ON in Barcelona (Spain) from 2008 to 2012, by a retrospective evaluation of electronic hospital records at the Hospital Clinic of Barcelona (population of 300,000 in the catchment area) matching the following ICD-9-CM codes as search terms: 377.3-optic neuritis; 377.30-optic neuritis, unspecific; 377.31-optic papillitis; 377.32-retrobulbar neuritis, acute; 377.39-other optic neuritis and "optic neuropathy". Demographic and clinical data were collected from records with a confirmed diagnosis of ON, including cases of idiopathic ON, multiple sclerosis, neuromyelitis optica and CRION. The prevalence of acute ON on 31 December 2012 was 2.75 cases per 100,000 people. The mean annual prevalence of acute ON during the 2008–2012 period was 7.87 cases per 100,000 person-year and the mean annual incidence rate was 5.36 cases per 100,000 person-years. The incidence of ON in Barcelona during 2008–2012 was higher than previously reported. This increase may reflect the evolution of diagnostic criteria, the use of a referral-center approach instead of a population-based approach, increased awareness of demyelinating diseases, latitude-related factors and possibly a true increase in its incidence.

Keywords Optic neuritis · Incidence · Prevalence · Epidemiology · Electronic health records · Spain

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Introduction

Optic neuritis (ON) is an acute inflammatory demyelinating disorder of the optic nerve [1]. ON occurs in isolation as monosymptomatic, idiopathic optic neuritis (iON), or in the setting of two central nervous system (CNS) demyelinating disorders, namely neuromyelitis optica (NMO) and multiple sclerosis (MS) [2]. Less commonly, ON may be associated with systemic immune-mediated disorders, chronic relapsing inflammatory optic neuropathy (CRION) or inflammatory and postvaccination responses [3].

The acute inflammation of the optic nerve in ON evolves over the period of 1 month, and as long as the inflammation decreases, vision typically improves. In fact, The Optic Neuritis Treatment Trial (ONTT) found that 85 % of participants recovered a visual acuity (VA) better than 20/25 after a 15-year follow-up [4]. Nevertheless, even though most patients may achieve almost complete recovery of visual acuity, many of them experiment lasting symptoms that make their daily life difficult [5]. ON frequently affects middle-aged people [3], and thus it may be a cause of significant disability for working people. Moreover, there is no conclusive evidence of the benefits of corticosteroids [6] or other immunotherapies [7] in the long-term recovery of normal VA, visual field or contrast sensitivity.

Since ON is an acute disorder, the annual incidence is more frequently quoted in publications than the prevalence. In Olmsted County, MN (USA), a point prevalence of 115 cases per 100,000 individuals was reported in 1991 for a history of ON [8]. Since this prevalence included any subject who had ever been diagnosed with ON from 1935 to 1991, it might represent an overestimation of the true prevalence. Indeed, it is notable that Olmsted County is a region with one of the highest prevalences of demyelinating diseases. Conversely, a point prevalence for ON of 5.5 cases per 100,000 was detected in 1971 [9], and the reported incidence rates range from 0.56 to 5.1 cases per 100,000 person-years [8–21]. However, the two most recent epidemiological surveys reported conflicting incidence rates of 0.83 [22] and 33 cases per 100,000 person-years in 2002–2004 [23], although these studies were carried out in Asian countries where the prevalence of demyelinating diseases differs significantly from that among the Caucasian populations in Europe and the US. Clearly, despite the impact of this disease, epidemiological data regarding the incidence of ON remain controversial.

Considering the future perspectives for new neuroprotective therapies for ON [24], it is important to update the figures of ON prevalence in order to provide information about how many patients would benefit from these therapies, especially considering the economic perspectives in an era of health budget constraints. This information will also be critical for the design of clinical trials for ON. Thus, the purpose of this study was to evaluate the incidence and prevalence of optic neuritis in the city of Barcelona (Spain) from 2008 to 2012.

Methods

We performed a hospital-based epidemiological study by carrying out a retrospective study to evaluate the prevalence and incidence of ON in the catchment area of the Hospital Clinic of Barcelona, a tertiary healthcare centre. The study period was from 1 January 2008 to 31 December 2012, and the Research Ethics Committee approved the study, with all participants providing their written informed consent.

Definition of demyelinating optic neuritis

The patients studied all met the inclusion criteria for ON, as defined in the ONTT [25], having referred to an acute or sub-acute loss of vision without evidence of metabolic, toxic, vascular, traumatic or compressive etiology, as well as the presence of one or more of the following symptoms or signs: eye pain that is worsened by eye movement; unilateral relative afferent pupillary defect (RAPD); visual field deficit or scotoma; impaired color vision; or optic disc edema. Edema in the retinal nerve fiber layer (RNFL) in peripapilar scans was evaluated by optical coherence tomography (OCT), while abnormal visual evoked potentials (VEPs) or gadolinium-enhancement in the optic nerve when studied by magnetic resonance imaging (MRI) were considered to ensure an accurate diagnosis in atypical or dubious cases. Recurrent ON was defined as a second ON episode in either eye occurring at least 1 month after the previous episode, as indicated elsewhere [26]. ON in the setting of a systemic immune-mediated disorder was excluded from the analysis. MS was diagnosed according to the MS criteria 2010 [27] and NMO according to the Wingerchuk [28] criteria. Chronic relapsing inflammatory optic neuropathy (CRION) was defined according to the first CRION description defined in 2003 [29]. Only new cases of ON during 2008–2012 were taken into account in our study, including incident idiopathic ON and incident ON in the setting of MS and NMO, but not where any previous episodes of ON occurred in the setting of these diseases.

Data source and management

The Hospital Clinic of Barcelona provides medical care to nearly 300,000 people living in the *Eixample* area of the city of Barcelona, Spain (the exact reference population is displayed in the Supplementary material S1). The Department of Epidemiology at the Hospital Clinic provided accurate and updated information about the population of the catchment area during the study period 2008–2012. We first searched the electronic health records (EHR) of in-patients and out-patients at the hospital for the following ICD-9-CM codes: 377.3 (optic neuritis), 377.30 (optic neuritis, unspecific), 377.31 (optic papillitis), 377.32 (retrobulbar neuritis, acute) or 377.39 (other optic neuritis). We also added to these codes "optic neuropathy" as a search-term for our automated search tool to collect

possible non-coded cases of ON. The EHR is fully integrated within the SAP® Healthcare solution. All episodes may be associated with one or more diagnoses, and they may be coded by physicians or by the coding staff at the Clinical Documentation Department, using ICD9 (compulsory by law in Spain), or simply with a free text description in Spanish or Catalan. Two methods were used to query the system. The first method involved selecting the coded fields and making the query with the corresponding ICD9 code, which identified all episodes. The second method involved querying the free-text field with expressions that match the most common expressions for the disease, e.g., optic neuritis, optic papillitis, retrobulbar neuritis and optic neuropathy. We used the common Boolean operators and wildcards in order to retrieve the best matches. This second method requires reviewing the EHR to ensure an accurate diagnosis. In addition, the ophthalmological and neurological examinations, as well as laboratory and imaging results in all the medical records from the study period that matched the aforementioned codes or search-terms were reviewed by an expert neurologist (EM-L) to determine whether these cases fulfilled the ON diagnostic criteria. All patients with previous demyelinating diseases (MS or NMO) are followed at the MS center in our hospital and any new episode of ON is recorded in their EHR. Finally, demographic and clinical data were collected from the records with confirmed ON, including sex and date of birth. The aim of this project was to evaluate the incidence and prevalence of ON and not to provide a detailed clinical profile of ON in our area. For this reason, we collected limited data on the clinical ophthalmological features, which included the date of ON diagnosis, visual acuity (VA) after 6 months of the ON onset, a measure of visual outcome, and any recurrent episodes of ON. Additionally, we also considered the subsequent diagnosis of MS or NMO, and the presence of white matter lesions in brain MRI, which have been described as the strongest predictor for the development of MS [30].

Statistical analyses

Quantitative data are presented as the means and standard deviations (SD), whereas we used frequencies and proportions to represent the qualitative data. The point prevalence of acute ON was determined as the number of subjects with acute ON per population on 31 December 2012. The annual prevalence of acute ON was determined as the number of patients having acute ON per population during a 12-month period. ON is an inflammatory phenomenon with a duration of 6 months (1 month for the inflammatory phase and up to 6 months for the recovery phase), after which visual symptoms may remain

Table 1 Etiological diagnosis of optic neuropathies (including ON) in our study

Diagnosis	*N* cases
Optic neuritis	82
Idiopathic optic neuritis	26
Optic neuritis in the setting of multiple sclerosis	48
MS diagnosed prior to ON episode	16
ON with demyelinating inflammatory lesions in brain MRI	8
ON leading to the diagnosis of MS	24
Optic Neuritis in the setting of neuromyelitis optica	2
NMO diagnosed prior to the ON episode	2
ON leading to the diagnosis of NMO	0
Optic neuritis in the setting of chronic relapsing idiopathic optic neuropathy	2
ON leading to the diagnosis of CRION	2
Optic neuritis in the setting of systemic inflammatory diseases	4
Vasculitis ANCAs+	2
Sarcoidosis	1
HIV (immune-mediated; not infectious)	1
Optic neuropathy	67
Anterior ischemic optic neuropathy	38
Arteritic	10
Non-arteritic	28
Compressive optic neuropathy	6
Meningioma	3
Oligodendroglioma	1
Inflammatory tissue (rheumatoid arthritis and Wegener)	2
Toxic-nutritional optic neuropathy	5
Drugs (etambutol/highly active antiretroviral therapy)	2
Alcohol and vitamin B deficiency	3
Traumatic optic neuropathy	1
Hereditary optic neuropathy	1
Glaucoma	2
Oculomotor neuropathy	4
Ischemic	2
Compressive	1
Central nervous system lesion (MS)	1
Papilledema due to benign intracranial hypertension	2
Undiagnosed progressive optic neuropathy	8
Other causes	32
Ophthalmological disease without optic nerve involvement	14
Neurorretinitis and posterior uveitis (Toxoplasma)	2
Ischemic retinopathy (1 venous occlusion/2 arterial occlusions)	3
Diabetic retinopathy	1
Uveitis (idiopathic/Behçet's/MS)	3
Cataract	2
Refractive errors	2

Table 1 continued

Diagnosis	*N* cases
Rhegmatogenous retinal detachment	1
Visual cortex structural or functional abnormalities	4
Posterior cortical atrophy	1
Metastasis (microcytic lung neoplasia)	1
Intracerebral arterio-venous vascular malformation	1
Migraine	1
Absence of ophthalmological disorder	14
Erroneous codification[a]	12
Psychogenic visual loss	2

MS Multiple sclerosis, *NMO* neuromyelitis optica, *ON* optic neuritis, *CRION* chronic relapsing inflammatory optic neuropathy, *HIV* human immunodeficiency virus, *ANCA* anti-neutrophil cytoplasmic antibodies

[a] These patients did not suffer any ophthalmological disease and there were no vision-related complaints in their records

permanently disabled. Accordingly, the 2008 prevalence rate was determined as the number of subjects with a new diagnosis of ON from 1 July 2007 to 31 December 2008, since the patients diagnosed with acute ON after 1 July 2007 would be in the acute phase during 2008. The same approach was used for other annual prevalence rates of acute ON during the study period. The annual global incidence rate of ON is the number of new diagnoses of ON per 100,000 person-years during the study period. We calculated the total annual and sex specific incidence rates from 2008 to 2012. All statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc, Chicago, IL).

Results

Data management and ON ascertainment

We found 609 EHRs that matched the search terms and codes. We excluded 90 duplicates and 337 records with a code or search terms that did not fall within our study period (2008–2012), as well as one patient with ON during 2008–2012 who did not reside within the Hospital's catchment area. Thus, 181 EHRs with ICD-9-CM codes (377.3; 377.30; 377.31; 377.32 or 377.39) or containing the term "optic neuropathy" were studied (Table 1 shows the definitive diagnosis for those patients where available). The ophthalmological and neurological data for all of these patients was reviewed, and briefly, 99 patients had diseases other than optic nerve or optic neuropathy, whereby anterior ischemic optic neuropathy (AION) was the most commonly found differential diagnosis. We found 82 patients with ON, of which 26 were iON, two cases were diagnosed as CRION, 50 as ON in the setting of brain

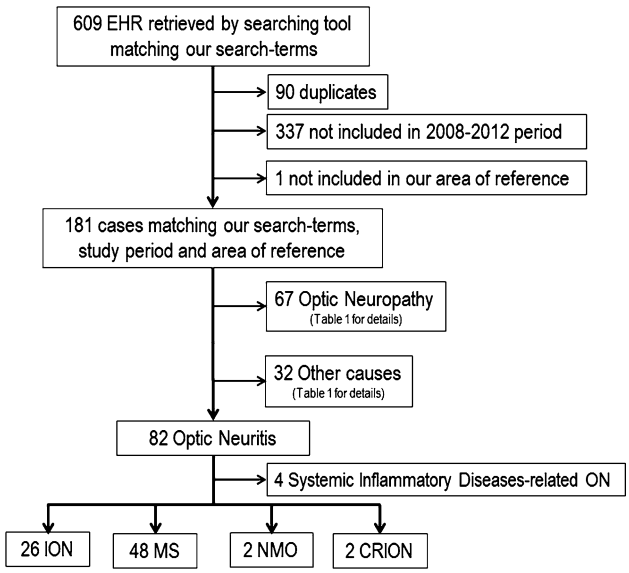

Fig. 1 Flow-Chart of the participants in the study. We identified 609 EHR that matched the search-terms and codes. We excluded 90 duplicates and 337 records with a code or search-terms not included in our study period (2008–2012) and one patient with ON during 2008–2012 who did not fall in the Hospital Clinic's catchment area. Of the remaining 181 EHR with ICD-9-CM codes (377.3; 377.30; 377.31; 377.32 or 377.39) or the search term "optic neuropathy", 67 patients were excluded since they had different causes of optic neuropathy, with anterior ischemic optic neuropathy (AION) being the most common of these differential diagnoses. A further 32 patients were excluded for other causes, such as ophthalmological disease without optic nerve involvement, visual cortex abnormalities or the absence of ophthalmologic disorders

inflammatory diseases (namely NMO and MS), and four were patients with ON in the setting of systemic immune-disorders. This latter group was excluded from the study of incidence in accordance with our study criteria. Figure 1 shows a flow-chart of the participants included in our study.

Demographic and clinical features of the study population

The study population included 78 patients with incident ON from 2008 to 2012, 55 of whom (71 %) were females, while the mean age at ON onset was 36 ± 10 years (Table 2). ON recovery was defined as good (high contrast VA >20/25) for 81 % of the patients after a 12-month follow-up, although four (5 %) patients had a VA less than 20/400, the VA considered by the World Health Organization (WHO) as blindness [31]. Similarly, most patients recovered their color vision well and only 12 % presented acquired dyschromatopsia. However, no data was available regarding other kinds of visual impairment or quality of vision, which impedes a full assessment of visual disability after ON. In terms of the etiology of ON, we found 26

Table 2 Demographic and clinical features of incidence ON

Sex Female *n* (%)	55 (71)
Age at onset of optic neuritis (years)	36 ± 10
Visual acuity recovery *n* (%)[a]	
Visual acuity ≥ 20/20	45 (62)
Visual acuity between 20/20 and 20/25	14 (19)
Visual acuity < 20/400	4 (5)
Color vision recovery *n* (%)[b]	
Acquired dyschromatopsia	12 (18)
Brain MRI demyelinating lesions (0–6 months after ON) *n* (%)	48 (61)
MRI in the setting of MS	16 (33)
Dissemination in space and time	18 (37)
Dissemination in space	11 (23)
Not meeting dissemination in time/space dimensions	3 (6)
Definitive diagnosis *n* (%)	
Idiopathic	26 (33)
MS	48 (61)
NMO	2 (3)
CRION	2 (3)

MRI Magnetic resonance imaging, *MS* multiple sclerosis, *NMO* neuromyelitis optica, *CRION* chronic relapsing inflammatory optic neuropathy

[a] $n = 73$ (five patients did not return to the ophthalmologist for the follow-up visit)

[b] $n = 65$ (five patients did not return to the ophthalmologist for the follow-up visit, seven patients had poor VA so the color vision test was invalid, and one patient was diagnosed as having congenital bilateral mild dyschromatopsia)

patients with iON (33 %), two patients with CRION, ON associated with NMO in two patients and ON associated with MS in 48 (61 %). In the case of ON in MS patients, 16 patients (33 %) were diagnosed with MS before the episode of ON and 32 patients (67 %) suffered ON as a symptom of the onset of CIS/MS. Table 2 shows the demographic and clinical characteristics of the ON patients, while the demographic and clinical features of our cohort in function of the definitive ION, MS, NMO, CRION diagnostic criteria are displayed in Table S2 (Supplementary Material).

Prevalence of ON

The point prevalence of acute optic neuritis on 31 December 2012 was 2.75 cases per 100,000 people (3.25 for females and 2.20 for males). The mean annual prevalence of acute optic neuritis in our reference area during the period 2008–2012 was 7.87 cases per 100,000 person-years (10.50 for females and 4.90 for males: Table 3 shows the total and sex specific prevalence rates for the study period).

Table 3 Total and sex specific prevalence and incidence rates of ON in Barcelona (Spain) during 2008–2012

Prevalence rates of ON in Barcelona (Spain) 2008–2012

Study period	Prevalence rates per 100,000 persons			Age of group with peak prevalence
	Total	Male	Female	
2008	8.68	6.40	10.71	20–30 years
2009	7.31	5.93	8.54	30–40 years
2010	7.37	3.74	10.60	Bimodal: 20–30 and 40–50 years
2011	7.83	4.35	10.92	30–40 years
2012	7.57	3.66	11.04	30–40 years

Incidence rates of ON in Barcelona (Spain) 2008–2012

Study period	Incidence rates per 100,000 person-years			Age of group with peak incidence
	Total	Male	Female	
2008	6.68	4.27	8.82	20–30 years
2009	3.83	3.70	3.94	25–35 years
2010	5.97	2.24	9.28	Bimodal: 20–30 and 40–50 years
2011	5.45	3.62	7.07	30–40 years
2012	4.82	2.93	6.49	30–40 years

Incidence rates of ON

The mean annual incidence of ON during the 5-year study period was 5.36 cases per 100,000 person-years (7.13 for females and 3.36 for males). The total and sex specific annual incidence rates from 2008 to 2012 are displayed in Table 3, and the annual incidence rate of isolated ON was 4.12 cases per 100,000 person-years (excluding the cases of ON in a setting of MS and NMO). The incidence rate of ON was higher in females than in males during the entire study period. Except for 2009, when we found a bimodal distribution for the age of onset, with a peak incidence between 20 and 40 years of age.

Rate of conversion to MS from ON

Of 82 ON episodes, 22 occurred in patients who were already diagnosed with systemic (four cases) or brain inflammatory diseases (18 cases) prior to the development ON. This left 60 isolated ON cases at diagnosis. One patient suffered three episodes of ON and was finally diagnosed with CRION. Two patients suffered two recurrent ON episodes and one patient, three recurrent ON episodes. Thus, these 60 cases correspond to 54 patients at risk of MS progression. The cumulative probability for MS progression for patients with monosymptomatic ON during the follow-up was defined (Fig. 2), and the cumulative probability for MS progression was nearly 30 % by 6 months and 45 % by the end of the follow-up.

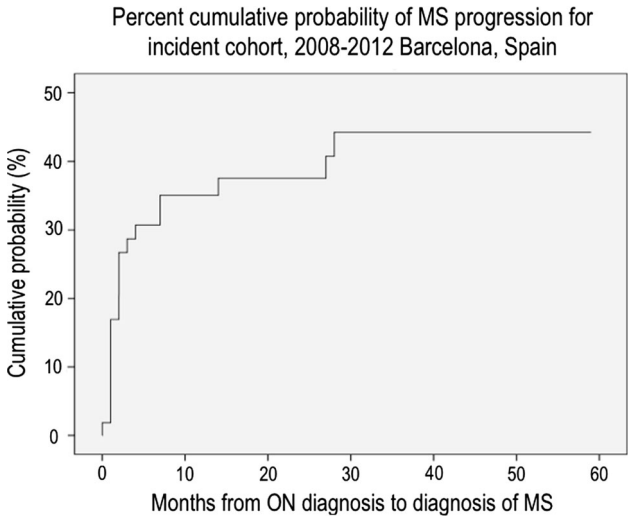

Fig. 2 Kaplan–Meier curves for the conversion of monosymptomatic ON to multiple sclerosis. The figure displays the cumulative probability of MS progression for those patients with monosymptomatic ON at the initial evaluation. The cumulative probability for MS progression was nearly 30 % by 6 months and 45 % by the end of follow-up

Discussion

In this hospital-based epidemiological study of ON, we found a mean annual incidence rate of 5.36 cases per 100,000 person-years during the period 2008–2012, and a mean annual prevalence of 7.87 cases per 100,000 population. The low number of cases and the seasonal nature of ON could explain the fluctuations observed in the sex-specific annual incidence and prevalence rates, as occurred particularly for women in 2009. The cumulative probability for MS progression was 45 % for those with the maximum follow-up (60 months). Prior studies described slower trends to MS progression, since MS progression was mainly based on clinical progression (new relapses) [8]. Currently, healthcare is more accessible and we repeat MRI studies to achieve an earlier diagnosis of MS in order to provide prompt treatment. For this reason, our study shows a faster rate of MS progression. Patients with demyelinating lesions in the initial evaluation were re-scanned within 3–6 months after the episode of ON to evaluate if the MRI criteria for MS diagnosis were fulfilled. This could explain the high rate of MS progression in the 6 months after the ON episode.

In our study, the mean age of ON onset was 36 years with a female/male ratio of 2.4. This clinical profile was similar to that identified in previous epidemiological surveys of ON incidence [8, 19, 20, 23], although little epidemiological data are available regarding prevalence rates. A point prevalence of ON of 115 cases per 100,000 persons was reported in 1991 in Olmsted County, MN (USA). However, this study included everyone with a prior history of ON diagnosis during a 56-year period [8]. A point prevalence of ON of 5.5 cases per 100,000 was found in 1971, although it was not specified if this referred to only acute ON [9] (a review of the epidemiological surveys evaluating ON incidence rates can be found in Table 4). We found slightly higher incidence rates for both females and males than those reported previously in other epidemiological surveys [8–22], except for one conducted in Taiwan during 2000–2004 [23].

There may be several explanations for the epidemiological differences described in ON. First, we should consider the evolution of diagnostic criteria. Most of the epidemiological studies assessed monosymptomatic ON and specifically excluded ON in the setting of demyelinating diseases, namely MS and NMO [10, 12–22], which would lead to lower incidence rates. In our study, the mean annual incidence rate would be 4.12 cases per 100,000 person-years if we excluded the cases with prior demyelinating diseases, an incidence rate that is still higher than those reported previously, with the exception of that performed in Taiwan [23]. Second, previous rates may be underestimated in the light of current disease awareness. ON is frequently the onset symptom for MS [32] and there are many disease-modifying therapies that halt the progression of MS, making early diagnosis of great importance. For this reason, most ON patients are referred to ophthalmologists or neurologists to rule out MS. Many of the aforementioned studies were carried out in a time period in which there was no treatment for MS and diagnosis at that time was significantly more restrictive than now. Therefore, it is possible that only the most severe cases or those that did not recover spontaneously were referred to specialists from a primary healthcare setting. Moreover, healthcare is now more accessible to the general population than before (e.g. MRI studies) and the general population, especially middle-aged individuals, is now more concerned about their health. Third, different sampling methods may partially explain these differences. The use of EHRs simplifies case identification in comparison with traditional written medical records or disease registries self-collected by physicians. Finally, MRI of the optic nerve, VEP and OCT in particular allow the ophthalmologist to diagnose atypical or very mild cases of ON that may have been misdiagnosed a few years ago.

If we consider the epidemiological survey carried out in Taiwan, it seems that all cases of ON were included in this study, not only the ON associated with all types of demyelinating diseases, but also those associated with systemic immune-mediated disorders. The prevalence of vasculitis, granulomatosis and other systemic diseases differs significantly between Asian and European (Caucasian) populations. Moreover, authors recognized that cases

Table 4 Review of epidemiological surveys of ON

Place and study period	Main condition under study	Average annual Incidence per 100,000			Age of group with peak incidence
		Female	Male	Total	
Taiwan: 2000–2004 [19]	iON + demyelinating ON (MS/NMO) + ON in systemic immune disorders	41	25	33	30–34 45–49
Singapore: 2002–2004 [18]	iON	–	–	0.83	–
Split-Dalmatia County, Croatia: 1985–2001 [17]	iON	2.2	1.1	1.6	20–29
Rijeka County, Croatia: 1977–2001 [16]	iON	1.36	0.82	2.18	25–29 (F) 30–39 (M)
Stockholm, Sweden: 1990–1995 [15]	iON	2.28	0.59	1.46	30–34 (F) 20–24 (M)
Japan: 1992–1993 [14]	iON	–	–	1.62	–
Olmsted County, USA: 1985–1991 [4]	iON + demyelinating ON (MS/NMO)	7.5	2.6	5.1	40–45
Olmsted County, USA: 1935–1991 [4]	iON + demyelinating ON (MS/NMO)	5.3	2.5	3.9	40–45
Sardinia, Italy: 1977–1986 [13]	iON	–	–	2.40	–
Two counties, Norway: 1972–1984 [12]	iON	–	–	1.40	–
Hannover, Germany: 1976–1977 [11]	iON	3.3	1.9	2.69	21–44
Uusimaa, Finland: 1970–1978 [10]	iON	3.2	1.5	2.4	30–39 (F) 40–49 (M)
Vaasa, Finland: 1970–1978 [10]	iON	2.8	1.8	2.3	20–29 (F) 30–39 (F)
Finland: 1967–1971 [9]	iON	1.15	0.71	0.94	20–29
Hawaii, USA: 1961–1971 [5]	iON + demyelinating ON (MS/NMO). Recurrent ON excluded	–	–	0.7	–
Israel: 1955–1964 [8]	iON	–	–	0.56	–
Carlisle, UK: 1955–1961 [7]	Retrobulbar ON	–	–	1.6	–
Rochester, Minn, USA: 1935–1964 [6]	iON	–	–	2.8	20–29

iON Idiopathic ON, *MS* multiple sclerosis, *NMO* neuromyelitis optica, *F* female, *M* male

of ON might be overdiagnosed given their data source [23]. Latitude-related factors may also explain the epidemiological variability described in ON incidence rates, as described in a study carried out on an Australian population [33]. Nevertheless, whether there is a true increase in the incidence of ON must be clarified in new prospective studies. However, recent data does support an increase in the prevalence and incidence of autoimmune diseases such as rheumatoid arthritis [34], and of demyelinating diseases, especially MS [35].

Our study has several limitations. First, we assess the incidence and prevalence of ON in an area of the city of Barcelona (Spain). This geographic area is a metropolitan area that may not be representative of the entire Spanish population. Second, this is a hospital-based epidemiological study, such that cases not referred to a specialist would not be included. However, as we have explained previously, the significant awareness regarding loss of vision, and demyelinating and autoimmune disease, and the relatively easy access to diagnostic tests nowadays (MRI, OCT), may decrease the differences between population and referral center studies. Some patients may be diagnosed with ON in the emergency room of other hospitals. However, according to health policies, non-urgent diagnostic testing, treatment and monitoring of patients should be done in the corresponding reference health centre.

Accordingly, we can identify patients with ON regardless of where the ON diagnoses were initially made. Our study also has several strengths, the first of which lies in our search strategy, which by being based on EHR offers an updated diagnosis. Second, diagnosis of ON was performed by trained neuro-ophthalmologists with full access to the diagnostic techniques (OCT, MRI and VEP) needed to reach an accurate diagnosis, even in dubious cases. Third, the EHR allows us to identify patients not included in the Hospital Clinic catchment area who received medical assistance in our hospital. For this reason, we excluded one patient with ON during 2008–2012, and excluding such patients is important to avoid overestimation.

In conclusion, we found higher incidence rates of ON than in previous studies. These differences may be explained by differences in disease ascertainment, but they also raise the question as to whether ON incidence is increasing. However, new longitudinal studies will be required to resolve this question. These increased incidence rates may be taken into account for future specific treatments for ON.

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Conflicts of interest Elena H Martínez-Lapiscina has received travel and accommodation expenses from Novartis, Teva, Sanofi Aventis, Lundbeck and Bayer for national and international congresses.Elena Fraga-Pumar has no conflicts of interest to disclose.Xavier Pastor has no conflicts of interest to disclose.Mónica Gómez has no conflicts of interest to disclose.Artur Conesa has no conflicts of interest to disclose.Raimundo Lozano-Rubí has no conflicts of interest to disclose.Bernardo Sanchez-Dalmau has received travel and accommodation expenses from Novartis for national and international congresses.Alvaro Alonso has no conflicts of interest to disclose.Pablo Villoslada has received consultancy fees from Roche, Novartis, MedImmune, TFS, Heidelberg Engineering and Neurotec Farma, and he is a shareholder in Bionure Farma.

Ethical standard The Research Ethics Committee of the Hospital Clinic of Barcelona reviewed and approved this study, which has been conducted following Helsinki recommendations and European Union and Spanish regulations.

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