Update on Optic Neuritis: An International View

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Abstract

Previously, optic neuritis was thought to be typical, ie idiopathic or multiple sclerosis (MS) related, associated with a good visual prognosis, or atypical, ie not associated with MS and requiring corticosteroids or plasma exchange for vision to recover. More recently, the importance of optic neuritis in neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein (MOG) antibody disease has become more appreciated. The results of the Optic Neuritis Treatment Trial (ONTT) has influenced how optic neuritis is treated around the world. For this review we surveyed the international literature on optic neuritis in adults. Our aims were first to find the reported incidence of optic neuritis in different countries and to ascertain what percentage of cases were seropositive for anti-aquaporin 4 and anti-MOG antibodies, and second, to document the presenting features, treatment and outcomes from a first episode of the different types of optic neuritis from these countries, and to compare the results with the outcomes of the ONTT cohort. From these data we have sought to highlight where ambiguities currently lie in how to manage optic neuritis and have made recommendations as to how future treatment trials in optic neuritis should be carried out in the current antibody testing era.

Introduction

The presentation, treatment and visual outcome of optic neuritis have been previously reviewed in *Neuro-Ophthalmology* in 2008 and 2011.[1,2] At the time of these reviews contemporary understanding was that optic neuritis was typical, ie idiopathic or multiple sclerosis (MS) related, associated with a good visual prognosis, or atypical, ie not associated with MS and requiring corticosteroids or plasma exchange (PLEX) for vision to recover. The atypical forms were felt to be more likely to be bilateral and more likely to relapse. They could be isolated, as in chronic relapsing inflammatory optic neuropathy (CRION), or associated with neuromyelitis optica (NMO) with its serological marker anti-aquaporin 4 (AQP4) antibodies.[1] Since then, new diagnostic criteria have been published defining NMO spectrum disorder (NMOSD),[3] in revising the MS diagnostic criteria[4] and in defining the role of anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies in central nervous system demyelinating disorders.[5] In addition, optic neuritis has recently been described as occurring as part of anti-glial fibrillary acidic protein antibody associated meningoencephalitis [6] and in association with anti-glycine receptor α1 subunit antibodies.[7] These antigens are expressed at high concentrations in the optic nerve, but further work is required to better understand if these antibodies are pathogenic or represent an epiphenomenon.

The nomenclature defining the different subtypes of optic neuritis continues to be refined and the different subtypes are listed in Table 1,[8-10] although most experts in the field would agree that there is currently no consensus as to these definitions.

Optic Neuritis Treatment Trial

Much of our knowledge about the natural history of optic neuritis and how to treat it has come from the Optic Neuritis Treatment Trial (ONTT). The ONTT recruited participants with a first episode of acute unilateral optic neuritis at a mean 5 days following the onset of visual symptoms.[11] Follow-up extended out to a remarkable 15 years.[12] The ONTT established that intravenous methylprednisolone (IVMP), 250 mg four times per day for 3 days followed by oral prednisone 1 mg/kg per day for 11 days, hastened the recovery of visual function following optic neuritis but did not affect final visual outcome compared with oral prednisone (1 mg/kg per day for 14 days) or oral placebo. The use of IVMP was also associated with a transiently lower risk of developing clinically definite multiple sclerosis (MS) for up to 2 years in those with demyelinating lesions on initial brain magnetic resonance imaging (MRI). In addition, the ONTT found that, surprisingly, treatment with oral prednisone was associated with an almost doubling of the risk of having a recurrence of optic neuritis in either eye within 5 years compared with taking IVMP or oral placebo.[11,13] This finding is, in absence of pharmacological data from the ONTT, difficult to explain biologically.

There are caveats when applying the results of the ONTT to the treatment optic neuritis in the clinic and in understanding the natural history of the disease. The trial was carried out in 15 institutions in the United States of America (USA).[12] The participants were 85.3% white Caucasian, 12.7% African American, 1.5% Asian and 0.4% Hispanic.[14] Only participants with a first episode of acute unilateral optic neuritis were included between the ages of 18 and 46 years. The major exclusion factors included: treatment for optic neuritis already instituted; previous diagnosis of optic neuritis; diagnosis or evidence of any systemic condition other than MS, that might cause optic neuritis, or for which corticosteroids would be contraindicated; evidence of optic disc pallor in the currently affected eye; ocular findings suggestive of a non-demyelinating cause for optic neuritis such as macular exudates, more than a trace of vitreous cells or iritis; pre-existing ocular abnormalities that might affect assessment of visual function; poor reliability indices on the Humphrey field analyser not exceeded in the eye with better vision; painless visual loss associated with disc swelling and either disc or peri-papillary haemorrhage or altitudinal (or other nerve fibre bundle) type visual field defect; myopia measuring >6 D or hyperopia or astigmatism

measuring 3 D in the affected eye; narrow angle glaucoma induced by pupillary dilation; intra-ocular pressure > 30 mmHg in the affected eye; participant receiving medication that may produce retinal or optic nerve toxicity; participant having received systemic corticosteroid treatment or corticotropin for any condition for any duration within the past 3 months or for > 7 days within the past 6 months; arterial blood pressure > 180 mmHg systolic or 110 mm Hg diastolic; heart rate >120/min or the presence of a pathological arrhythmia; and a blood glucose level > 11.1 mmol/L.[15] The reason for the restrictions were to try and be more specific about the diagnosis but also to exclude participants who would be put at risk from treatment with corticosteroids. Prior to enrolment into the trial all subjects had ocular and neurological examinations, MRI of the brain, anti-nuclear antibody and fluorescent treponemal antigen testing, and a chest radiograph.[11]

The study was therefore designed to be a pragmatic randomised controlled trial of corticosteroids in the treatment of acute optic neuritis and not a natural history study assessing optic neuritis in general. It was also carried out in an era prior to testing for anti-AQP4 or anti-MOG antibodies.

The dosage regimens of the corticosteroids in the ONTT were chosen based on what was currently been used in clinical practice when the trial was being designed. This was influenced by previous studies on optic neuritis and MS but there were no experimental data available at the time to decide on what should be the optimum dose of corticosteroids or the optimum duration of treatment.[16]

An international survey has shown that the results of the ONTT have influenced practice across the globe, although with considerable variation between countries.[17] As is the case for all randomised control trials, it has not been established that the management of optic neuritis as suggested by the ONTT is applicable to other populations and to those who fall outside the inclusion criteria.[18] In particular, this will include bilateral optic neuritis, optic neuritis in individuals of different ethnic heritage and optic neuritis associated with serum anti-AQP4 or anti-MOG antibodies.[19-21]

Aims of this review

The presentation and management of optic neuritis in children has been recently reviewed.[22] For this review we surveyed the international literature on optic neuritis in adults. Our aims were first to find the reported incidence of optic neuritis in different countries and to ascertain what percentage of cases were seropositive for anti-AQP4 and anti-MOG antibodies, and second to document the presenting features, treatment and outcomes from a first episode of optic neuritis from recent studies from different countries, to stratify them according to the type of optic neuritis, ie anti-AQP4 and anti-MOG seronegative optic neuritis (double antibody seronegative optic neuritis, ie idiopathic optic neuritis [ION] / multiple sclerosis associated optic neuritis [MSON]), neuromyelitis optica spectrum disorder associated optic neuritis (NMO-ON) and MOG antibody disease (MOGAD) associated optic neuritis (MOG-ON), and to compare the results with the outcomes of the ONTT cohort. From these data we sought to highlight where ambiguities currently lie in how to manage optic neuritis and to make recommendations as to how future treatment trials in optic neuritis should be carried out in the current antibody testing era.

Search strategy

We first search PubMed using the terms “optic neuritis” and “incidence” to find studies reporting optic neuritis incidence. To assess recent publications on optic neuritis in the antibody testing era we searched for published studies on optic neuritis in PubMed from 2008 up to March 2021. The search terms used were “optic neuritis”, “anti-aquaporin 4” and “anti-MOG”. Articles here were selected that reported the percentage of cases of a first episode of optic neuritis cases that were positive for serum anti-AQP4 and anti-MOG antibodies. Further articles were selected that recorded the presenting features, treatment

regimen and outcome of a first episode of optic neuritis according to the antibody status of the subject. Additional articles identified through the references lists of searched articles were also screened for relevancy and included in this review. Articles published in languages other than English or those that were not available as full text were excluded.

Incidence of optic neuritis and percentage of cases that are positive for anti-AQP4 and anti-MOG antibodies

Data on the reported incidence of optic neuritis from different countries are presented in Table 2.[23-46] Comparison of historical data, including countries with multiple reports, was facilitated by documenting the calendar years studied. The proportion of unselected subjects with their first episode of optic neuritis that were seropositive for anti-AQP4 and anti-MOG antibodies from the published studies from around the world are listed in Tables 3[10,27,34,47-63] and 4,[10,27,34,47,49,56,58,61,63-65] respectively. These include data from stored serum samples for a proportion of the subjects in the ONTT.[47]

The data from the Tables 2 to 4 were used to calculate national aggregate data, which are presented in Figures 1 to 3 for undifferentiated optic neuritis, anti-AQP4 and anti-MOG seropositive optic neuritis, respectively. For illustration of the global view in the figures, only one study was shown per country, which was either the most recent or the largest. Visualisation of these data show that, there is, in general, a West to East effect. The latitude effect that is seen with MS incidence cannot be ascertained for optic neuritis from these data,[66] mainly due to the paucity of studies from Latin America, Africa and the Middle East. Optic neuritis as a whole seems to be more common in the USA and Europe than in Asia.

Some of the variability in the incidence data may be explained by different methodologies used in case ascertainment, such as whether this was by population diagnostic coding or by hospital-based diagnosis. Diagnostic coding may be subject to inaccuracies in diagnosis since the diagnosis in each case reported is usually not checked. The hospital-based studies may suffer from referral bias, particularly if the hospitals are tertiary or quaternary centres. The study by Woung et al. from Taiwan stands out as an outlier with a reported annual incidence of optic neuritis of 33 per 100,000/year.[43] This may well be because it relied on national health insurance coding data, whose accuracy should be questioned, especially since the cumulative incidence of MS over 5 years of the study after a new diagnosis of optic neuritis was only 0.78%. In comparison, in a study from South Korea, which should have similar conversion rates to MS as Taiwan, the cumulative conversion rate to MS after optic neuritis over 7 years was estimated to be 10.6%.[44]

The testing protocol for anti-MOG antibodies was fairly consistent between the studies, however there was some variation in how the anti-AQP4 antibody testing was performed. It has been reported that all of the assays have high specificities, however the sensitivity of the radioimmuno-precipitation assay (RIPA) is 62.8%, compared with 76% for the fluorescence-based immunoprecipitation assay and 78% for cell-based indirect immunofluorescence assay.[50] Most studies, however used the latest cell-based assays so it is possible to draw reliable conclusions as to the variability across countries in the presence of these antibodies in cases of optic neuritis.

These studies suggest that in "Western" countries with predominant white Caucasian populations, the proportion of optic neuritis cases having serum anti-AQP4 or anti-MOG antibodies is low, although the Ducloyer et al. study appears to be an outlier with 12.7% prevalence of anti-MOG antibodies.[49] No data apart from geographical are given in that study regarding the population studied and it was limited to those centres with access to testing, which could have lead to inclusion bias. The proportion having either antibody appears to be much higher in the Far East and appears to correlate with the lower prevalence of MS in this region (Tables 3 and 4; Figures 2 and 3).[66] Seropositivity for anti-MOG is high

in Argentina (Table 4, Figure 3), but a convincing latitude effect for anti-AQP4 or anti-MOG antibodies again cannot be demonstrated due to the lack of studies from Latin America, Africa and the Middle East. The number of bilateral cases of optic neuritis were relatively low from all of the studies, but the results suggest that a greater proportion of bilateral cases than unilateral were anti-MOG seropositive, but this was less apparent for anti-AQP4 seropositive cases.

Population-based studies of NMOSD as a whole have also suggested higher prevalences in the Far East and in black populations than in white Caucasians from Europe and North America.[67] There have been insufficient studies on the prevalence of MOGAD as a whole to be able to draw any firm conclusions as to whether there are clear geographical variations in its prevalence. More studies are needed with a strict epidemiological approach, particularly from Africa, Latin America, the Middle East and the Asian subcontinent to further our understanding as to the variation in the incidence of optic neuritis and how the subtypes of optic neuritis relate to the national incidence of optic neuritis as a whole.

Comparison of the presenting features, treatment and outcome from optic neuritis related to country and antibody status

The presentations and visual outcomes from studies around the world for first episodes of different types of optic neuritis in predominantly adult populations are shown in Tables 5-7. The reason for looking at outcomes from first episodes of optic neuritis was to try and make the results of each study more easily comparable. The studies varied, though in terms of age of patients, gender balance and treatment, but also how the data were presented. We tried to present comparable data between the studies, although we have not performed statistical comparisons due to the apparent variability in the data. This was particularly the case for presenting and outcome visual acuities. We presented the proportion of subjects, where recorded, with good and poor visual acuities, expressed as a Snellen decimal (for ease of comparison), at presentation and at last follow-up. In most cases, it was not clear how case ascertainment occurred and since these were hospital-based studies there may have been some case ascertainment bias with more severe cases being referred to the hospitals where the studies were reported from, potentially leading to apparently poor outcomes in some of the case series.

The presenting features, treatment and outcome from studies of first episodes of double antibody seronegative optic neuritis compared with the results of the ONTT cohort are presented in Table 5.[10,14,15,49,58,63,68,69] These studies will have included subjects with both ION and MS-ON. Table 5 shows that mean age and gender mix were similar between studies. There was variable presence of pain, with one of the Chinese studies and the Japanese study reporting a low proportion of subjects with pain at onset of optic neuritis at 51.7% and 46.4% respectively.[58,63] The proportion with optic disc swelling were broadly similar across the studies, although it is not clear whether the presence of optic disc swelling influenced the likelihood of optic neuritis being diagnosed. These studies of double antibody seronegative cases had up to 23.3% prevalence of bilateral optic neuritis, although it was not clear how many of the bilateral cases in these studies had ION as opposed to MS-ON. Of note, a higher proportion of subjects in the international studies had poor vision at presentation compared with the ONTT cohort. This may partly relate to delay from onset of symptoms to presentation since it is known that vision loss in optic neuritis can progress over 2 weeks.[70] The ONTT initiated treatment within a mean of 5.1 days from the onset of visual symptoms with the maximum permissible delay being 8 days.[11] The early presentation in the ONTT may therefore partly explain the smaller proportion of patients with poor vision at presentation, although none of the other studies in Table 5 reported the time since onset to the first examination or initiation of treatment. The treatment administered was broadly similar between the studies with all, where reported, employing high dose intravenous corticosteroids, with or without a subsequent lower dose oral corticosteroid taper. One study treated a proportion of their patients with PLEX, al-

though neither detailed indications for its use nor the number of exchanges employed.[69] A higher proportion of patients in the ONTT had good visual acuity outcomes compared with the other international studies and there was a higher proportion in the international studies having poor outcomes, despite broadly similar treatment strategies employed between them and the ONTT.

The presenting features, treatment and outcome from studies of first episodes of NMO-ON are presented in Table 6.[10,48,55,58,59,63,69,71-75] The data show that the age at presentation was similar to the double antibody seronegative optic neuritis subjects but the proportion of females affected appeared to be higher in most studies. The proportion with pain at presentation also seemed to show a similar geographical distribution to double antibody seronegative optic neuritis with fewer reporting pain in China and Japan, although one study from Thailand had a very low percentage (19.0%) reporting pain at presentation.[73] In general, compared with double antibody seronegative optic neuritis, there were fewer cases with optic disc swelling but a higher proportion, at about a third, who had bilateral loss of vision at onset. The proportion of patients with presenting visual acuities of ≤ 0.1 were generally much higher than for double antibody seronegative optic neuritis. The studies employed similar corticosteroid dosages and routes of administration to the ONTT with variable use of subsequent immunosuppression. Three of the studies employed PLEX but the indication for its use, the delay to its initiation or the number of exchanges used were not reported in any of the studies.[63,71,74] The visual acuity outcomes were much worse than for double antibody seronegative optic neuritis, despite similar treatment regimens in most cases. The delay from first visual symptoms to the initiation of treatment was only reported in two studies: one from the United States and Thailand where the mean delay was 13.8 and 13.6 days respectively;[71] and another one from Thailand where the median delay was 4 days (range 1-60 days).[74]

The presenting features, treatment and outcome from studies of first episodes of MOG-ON are presented in Table 7.[10,49,58,63,75-81] The age at onset seemed broadly similar to the studies on double antibody seronegative ON and NMO-ON but the proportion who were female was less. There was a similar proportion with pain at onset compared with double antibody seronegative optic neuritis but more subjects had optic disc swelling and bilateral onset compared with the other two groups. The severity of visual acuity loss at onset was similar to the studies on NMO-ON, however the outcome visual acuities were better than for NMO-ON and more in line with outcome visual acuities reported for double antibody seronegative optic neuritis. The treatment regimens were similar to the other two groups with five studies also employing PLEX, again without detailed descriptions of the indications or the number of exchanges reported.[63,76-78,80] None of the studies reported the delay from onset to the initiation of treatment.

Discussion

Optic neuritis is a worldwide disease, but the distribution of the cases of ION/MS-ON versus NMO-ON and MOG-ON varies across the world, with increased incidence of the latter two in the Far East, although there remains a paucity of studies on it from some areas, notably Africa, the Middle East and Latin America regarding its epidemiology, the relative prevalence of NMO-ON and MOG-ON, its clinical features and the response to treatment.

The treatment regimens chosen in the studies we have reported have been influenced by the ONTT, yet the visual outcomes were often worse than in non-Western countries for double seronegative optic neuritis (Table 5). There may be differences in the timing of administration of and the response to corticosteroid treatment in the cohorts between the different countries reported in Table 5. The results from Table 6 show that after a first episode of optic neuritis the visual recovery is worse for NMO-ON than for double antibody seronegative optic neuritis and MOG-ON, although there are studies that suggest that up to 20% of patients with MOG-ON have poor long-term visual outcome.[75,82] The

ONTT regimen may be insufficient to treat optic neuritis in every ethnic group as well as NMO-ON and MOG-ON as the relatively poor visual outcomes seen in Tables 5-7 compared with the ONTT cohort attest. It has been previously proposed that higher doses and longer term treatment with corticosteroids should occur in Chinese subjects with optic neuritis.[19]

None of the studies reported above employed high dose oral corticosteroids to treat optic neuritis. A study from Canada of unselected optic neuritis cases found that there was no significant difference in visual acuity or visual evoked potential P100 latency between those treated with IVMP 1 g/day for 3 days and those treated with a bio-equivalent dose of 1250 mg/day oral prednisone for 3 days.[83]

The variation in prognosis may also be related to delay in initiating corticosteroid treatment as it has been argued that even a delay of 5 days to the initiation of treatment may be too long and could lead to worse outcomes in all kinds of optic neuritis,[84,85] although it is impossible to compare the other studies in Table 5 to the ONTT as they did not report the delay to treatment. For both NMO-ON and MOG-ON it has been reported in other studies that delay to onset of corticosteroid therapy is important in governing prognosis for visual recovery.[21,86,87] Conducting a trial to investigate the effects of delay to treatment will not be easy as there are often delays in subjects presenting with optic neuritis. In addition, all the studies have reported delay as being from onset of visual symptoms, although pain often precedes this by a few days,[70] which will be when the disease process will have started. It has been proposed that such a trial to investigate the effects of delay to treatment could be carried out on subjects with relapsing optic neuritis who can be primed to represent early on first recurrence of symptoms.[85] The results from a small case series have suggested that treatment with high dose corticosteroids at the onset of pain may prevent loss of vision from occurring.[88]

Although PLEX was employed in a number of the studies reported above with all types of optic neuritis, it is not clear from these results whether it made a difference, mainly since the indication for its use, the delay to treatment onset and the number of exchanges that occurred were not reported. The subjects receiving PLEX were likely those that had a poor response to corticosteroids. A recent open label study of all NMO relapses (with 66% being anti-AQP4 seropositive) reported that the probability of complete recovery decreased from 50% if PLEX started immediately to 1 - 5% if it started at day 20, suggesting therefore that the time to initiation of PLEX is the key factor in determining the response to it.[89] Because PLEX removes IgG from the serum the approach is likely to be most effective in individuals with a known, pathogenic antibody. In optic neuritis it is not yet certain that all auto-antibodies reported are pathogenic. The best evidence in this direction comes from translational studies demonstrating complement-mediated damage for AQP4 autoantibodies bound to astrocytes.[90] It may not be possible to access PLEX outside of major centres. Intravenous immunoglobulin (IVIG) is much more widely available and was employed in two of the studies reported here.[71,80] A recent study has shown benefit from 5 days of 400 mg/kg body weight/day IVIG versus a further 3 days of 1g/day IVMP with delayed IVIG treatment in steroid-resistant cases of optic neuritis. Of these, 71.9% were anti-AQP4 antibody positive but anti-MOG antibodies were not tested for.[91]

Phase II trials of novel neuroprotective and remyelinating agents in optic neuritis have shown beneficial effects on surrogate markers, such as optical coherence tomography (OCT) measurements of peripapillary retinal nerve fibre layer (pRNFL) thickness, although they were not powered to show an effect on vision scores.[92] The trials were performed in ION and MS-ON cases so it is not clear whether these agents will work in NMO-ON and MOG-ON.

In treatment trials, the OCT-derived surrogate markers, such as pRNFL and retinal ganglion cell layer thickness allow for trials to be adequately powered with smaller numbers of subjects, such that the use of OCT has now become the gold standard in Phase II trials in optic neuritis. Ultimately, though for any new treatment for optic neuritis to be widely adopted it has to show an effect on vision. High contrast visual acuity has a ceiling effect when there are high rates of recovery, so other more robust vision measures have been proposed to be used in future trials, such as low contrast visual acuity.[85]

Recent guidelines have been published regarding the investigation and treatment of acute optic neuritis.[93] However, we have shown from the studies reported here that there are still a lot of grey areas that need addressing requiring new treatment trials in optic neuritis, particularly for cases of NMO-ON, MOG-ON and for all optic neuritis cases in non-Western countries.[84] The main questions that need answering in these trials for each population are:

1) What is the optimum corticosteroid dosage regimen in terms of dose and duration of treatment, since the previous regimens employed have been largely empirical and based on the results of the ONTT?[16,19]
2) Are high dose oral and intravenous (IV) corticosteroids equivalent for the treatment of all kinds of optic neuritis? Oral treatment is cheaper and easier to administer than IV treatment and its use would lead to more widespread availability of corticosteroid treatment of optic neuritis in resource-poor countries.[83]
3) Is the delay to onset of corticosteroid treatment critical to visual outcome?[85] Although, as discussed above, such a trial would be difficult to conduct, if it did show a difference then it would have a lot of implications as to how quickly potential optic neuritis cases need to be investigated and treated.
4) In whom should PLEX be considered? Should it only be offered to those with a who are seropositive for a pathogenic autoantibody? Should it be delayed to give time for corticosteroids to work or should it be initiated immediately? What exchange regimen should occur? Access to PLEX can be difficult outside of major centres and therefore a trial of PLEX versus IVIG is also required to see if similar benefits can be obtained using the latter treatment.
5) Do novel neuroprotective and remyelinating drugs have a role in protecting axons and preserving vision in all types of optic neuritis? What is the optimal timing for initiation of these agents and is there a synergistic effect of combining different strategies?

Conclusion

With more data now showing that optic neuritis is not a homogeneous disease it is clear that the management cannot be by a "one size fits all" approach, which appears to have occurred in a lot of centres in many different countries as we have outlined. In the absence now of the answers to the above five questions it is important to judge each individual case of optic neuritis in the context of ethnicity of the patient, the severity of the impairment of vision at presentation and the access to investigations, such as MRI and serological tests. In cases that are anti-AQP4 or anti-MOG positive, or have imaging features suggestive of NMO-ON or MOG-ON prior to serological results becoming available,[93] or who are non-white Caucasian with severe impairment of vision at presentation then immediate treatment with high dose corticosteroids is indicated with a low threshold for escalation to PLEX, where available, in cases which fail to recover following initial corticosteroids.

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Declaration of conflicts or interest

The authors report no conflicts of interest.

Figure Legends

Figure 1
The incidence of optic neuritis from the different reported international studies. Aggregate data from Table 2 are presented. The graded blue colouring shows the national incidences. Data are absent from countries coloured pale yellow.

Figure 2
The proportion of unselected subjects with their first episode of optic neuritis being seropositive for anti-aquaporin 4 antibodies in the countries where the studies were performed. Aggregate data from Table 3 are presented. The graded blue colouring shows the national percentages. Data are absent from countries coloured pale yellow.

Figure 3
The proportion of unselected subjects with their first episode of optic neuritis being seropositive for anti-myelin oligodendrocyte glycoprotein antibodies in the countries where the studies were performed. Aggregate data from Table 4 are presented. The graded blue colouring shows the national percentages. Data are absent from countries coloured pale yellow.

Figure 1 The incidence of optic neuritis from the different reported international studies.
Aggregate data from Table 2 are presented. The graded blue colouring shows the national incidences.
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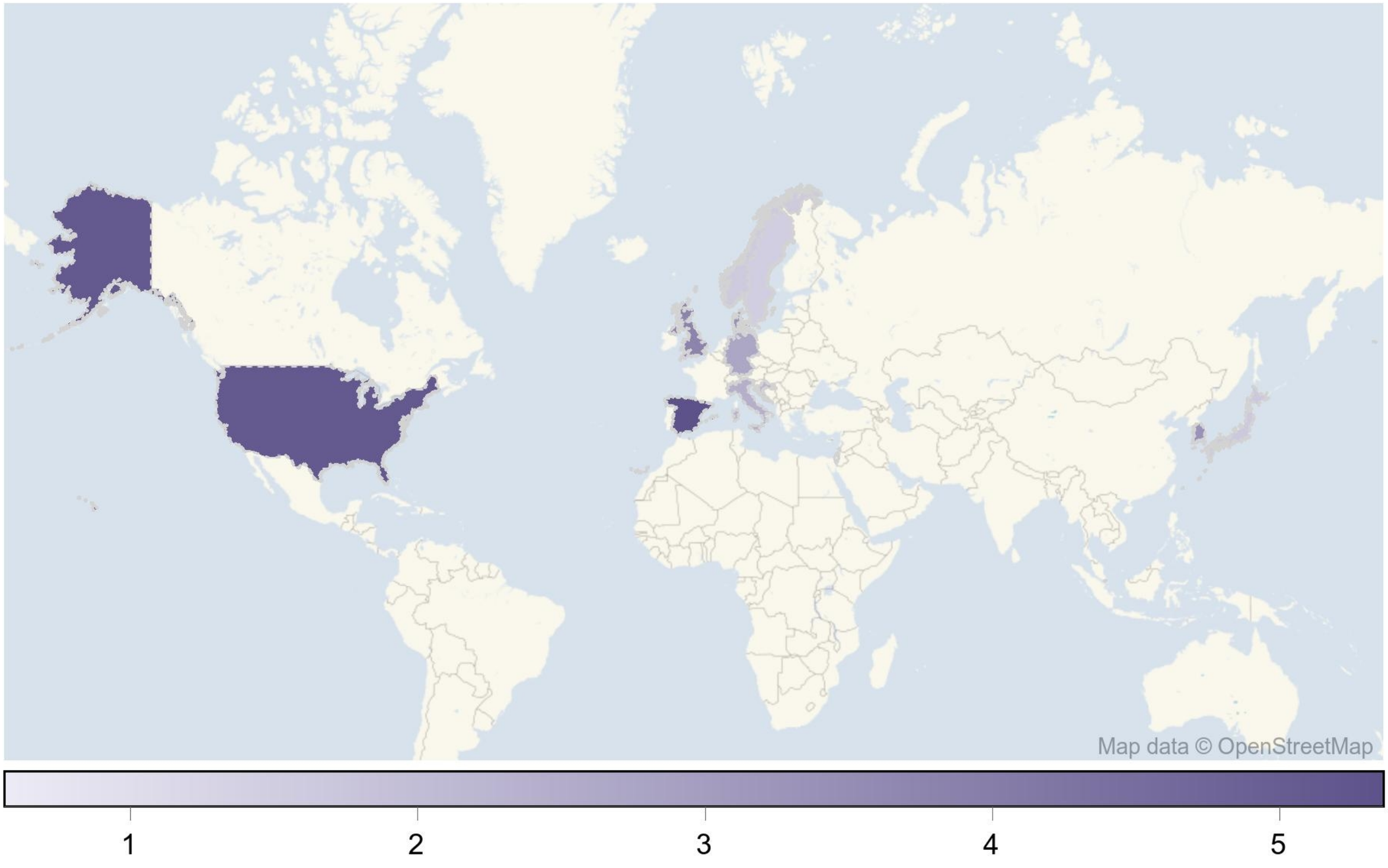

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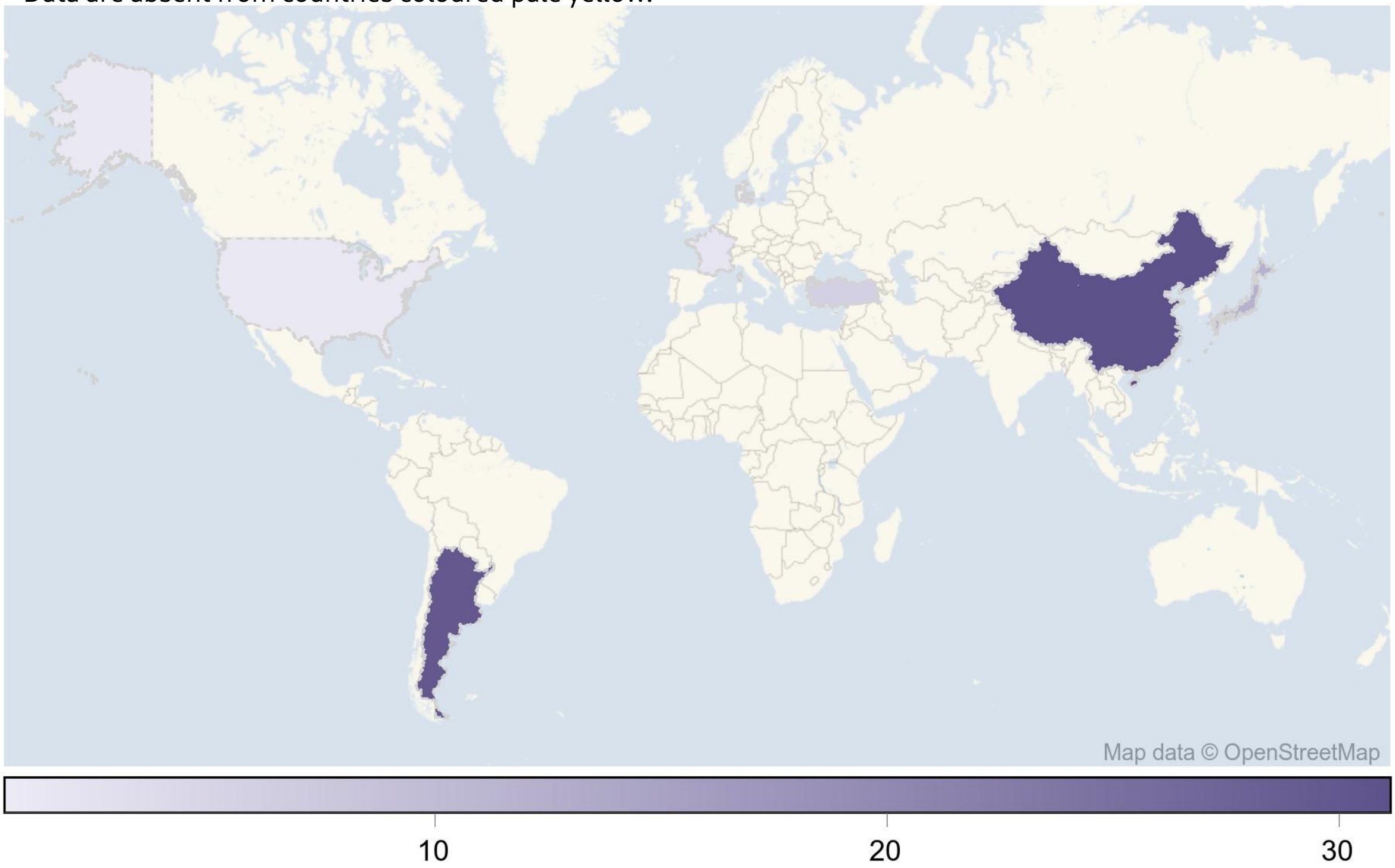
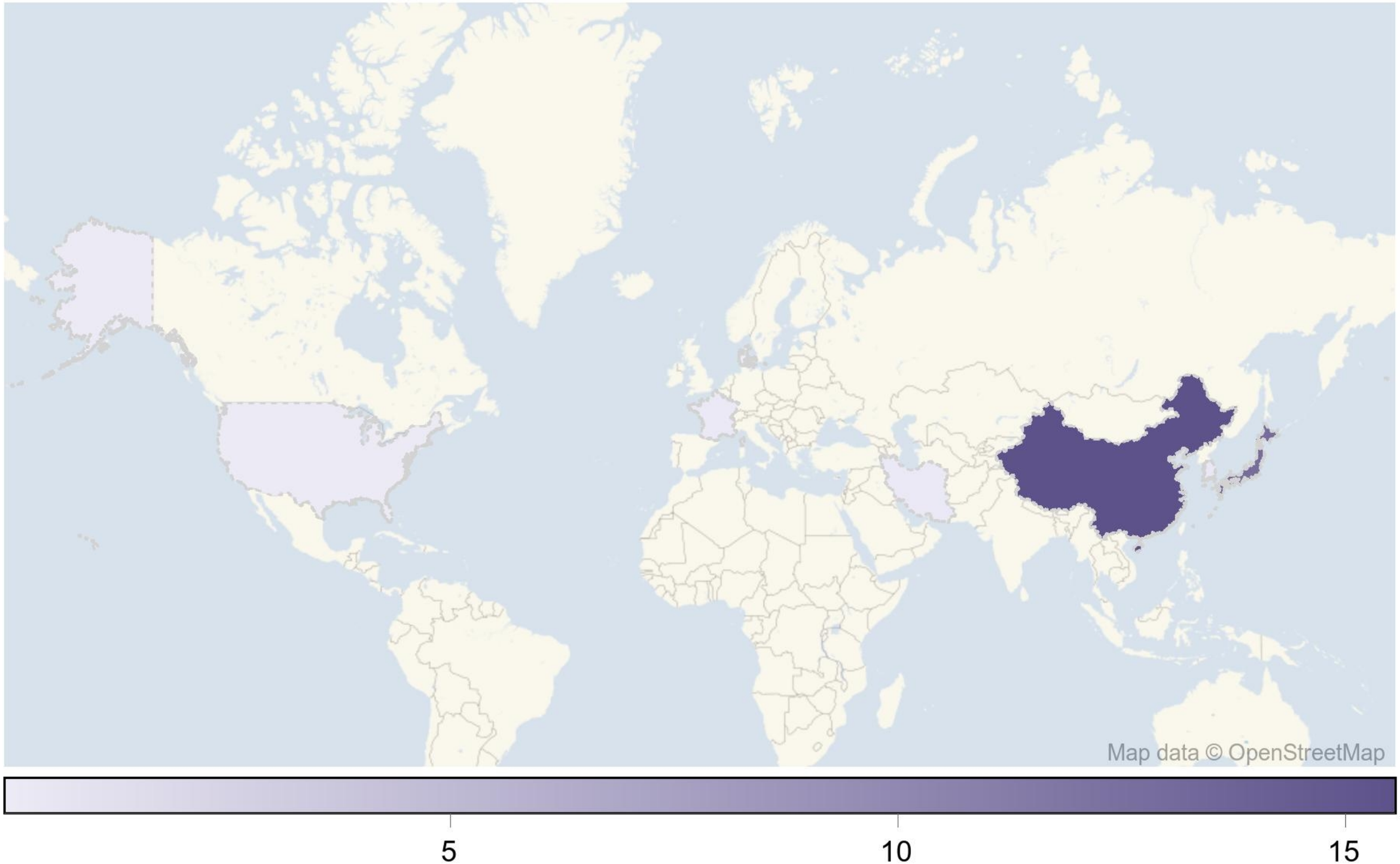


Percentage of optic neuritis cases having serum anti-aquaporin 4 antibodies (aggregate data from Table 3)

Figure 3 The proportion of unselected subjects with their first episode of optic neuritis being seropositive for anti-myelin oligodendrocyte glycoprotein antibodies in the countries where the studies were performed. Aggregate data from Table 4 are presented. The graded blue colouring shows the national percentages. Data are absent from countries coloured pale yellow.



Percentage of optic neuritis cases having serum anti-MOG antibodies (aggregate data from Table 4)

Type of optic neuritis	Definition
Isolated optic neuritis (ION)	A single episode of optic neuritis without imaging or serological evidence of an underlying disorder
Relapsing isolated optic neuritis (RION)	Spontaneously recovering relapsing isolated episodes of optic neuritis
Chronic relapsing inflammatory optic neuropathy (CRION)	Relapsing isolated episodes of seronegative optic neuritis that are corticosteroid dependent
Multiple sclerosis associated optic neuritis (MS-ON)	A first or recurrent episode of optic neuritis in association with multiple sclerosis
Neuromyelitis optica associated optic neuritis (NMO-ON)	A first or recurrent episode of optic neuritis in association with neuromyelitis optica spectrum disorder
Myelin oligodendrocyte antibody associated optic neuritis (MOG-ON)	A first or recurrent episode of optic neuritis in association with myelin oligodendrocyte glycoprotein antibody disease

Table 1: Clinical subtypes of optic neuritis

Country	Study period	At risk population	Ethnic distribution of at risk population	Annual incidence in adults
USA - Hawaii[23]	1961 - 1970	516,253	48.2% Oriental, 21.8% Hawaiian-mixed, 20.9% WC, 9.0% WC-Oriental	0.7 per 100 000 population / year
USA - Rochester, Minnesota[24]	1945 - 1954	30,000	NR	5.0 per 100,000 population / year
USA - Rochester, Minnesota[25]	1935 - 1964	NR	NR	3.5 per 100,000 population / year
USA - Olmsted County, Minnesota[26]	1985 - 1991	718,529	NR	5.1 per 100,000 population / year
USA - Olmsted County, Minnesota[27]	2000 - 2018	NR	86% WC	4.0 per 100,000 population / year
UK - Carlisle[28]	1955 - 1961	71,101	NR	1.4 per 100,000 population / year *
UK[29]	1995 - 2019	10,937,511	86.9% WC, 5.3% South Asian, 3.6% Black, 2.7% Mixed, 1.4% Other ∮	4.46 per 100,000 person-years
Spain - Eixample area of Barcelona)[30]	2008 - 2012	nearly 300,000	NR	5.36 per 100,000 person-years
Norway - Troms and Finnmark[31]	1972 - 1984	225,073	88.4% Norwegian, 11.6% Lapp	1.55 per 100,000 population / year
Germany - Hanover[32]	1976 - 1977	555,589	NR	2.69 per 100,000 population / year

Country	Study period	At risk population	Ethnic distribution of at risk population	Annual incidence in adults
Italy - Sardinia[33]	1977 - 1986	336,651	NR	2.40 per 100,000 population / year
Denmark - Region of Southern Denmark[34]	2014 - 2016	993,563	NR	3.28 per 100,000 person-years
Sweden - Stockholm County[35]	1990 - 1995	1,669,840	89.4% Nordic, 3.5% Asia, 1.3% Southern Europe, 0.9% Africa, 4.9% Other Countries	1.46 per 100,000 person-years
Croatia - Rijeka County[36]	1977 - 2001	NR	NR	2.18 per 100,000 population / year
Croatia - Split-Dalmatia County[37]	1985 - 2001	463,676	NR	1.6 per 100,000 population / year
Finland[38]	1967 - 1971	4,708,546	NR	0.94 per 100,000 population / year
Finland - Uusimaa[39]	1970 - 1978	1,111,067	NR	2.2 per 100,000 population / year
Finland - Vaasa[39]	1970 - 1978	428,122	NR	2.5 per 100,000 population / year
Finland - Helsinki and Uusimaa[40]	2008 - 2012	1,530,000	NR	3.0 per 100,000 population / year
Israel[41]	1955 - 1964	1,858,841	35.9% Israeli, 35.8% European, 28.4% Afro-Asian	0.56 per 100,000 population / year

Country	Study period	At risk population	Ethnic distribution of at risk population	Annual incidence in adults
Singapore[42]	2002 - 2004	3,487,000	76.0% Chinese, 13.7% Malay, 8.4% Indian, 1.9% Other	0.83 per 100,000 population / year
Taiwan[43]	2001 - 2004	191,761	NR	33 per 100,000 population / year
South Korea[44]	2012 - 2016	37,781,220	NR	3.29 per 100,000 population / year
South Korea[45]	2011 - 2017	50,000,000	NR	2.21 per 100,000 population / year
Japan[46]	1992 - 1993	NR	NR	1.62 per 100,000 population / year

Table 2: Incidence of undifferentiated optic neuritis cases from different countries listed from West to East starting from the United States of America

* Termed “retrobulbar neuritis”

∮ Where ethnicity data were available - data were missing for 6,031,767 (55.1%) of the total at risk population

NR = Not reported; UK = United Kingdom; USA = United States of America; WC = White Caucasian.

Country	Ethnicity of subjects	Number of subjects	Anti-AQP4 antibody assay method	Proportion (%) anti-AQP4 antibody positive amongst all optic neuritis cases	Proportion (%) anti-AQP4 antibody positive amongst unilateral optic neuritis cases	Proportion (%) anti-AQP4 antibody positive amongst bilateral simultaneous optic neuritis cases
USA (ONTT cohort)[47]	88.1% WC	177	Live flow cytometry CBA	0/177 (0%)	0/177 (0%)	N/A
USA[27]	NR*	105	Live flow cytometry CBA	3/105 (2.9%)	2/NR	1/NR
Argentina[48]	NR	57	Tissue-based IIFA	17/57 (29.8%)	11/39 (28.2%)	6/18 (33.3%)
France[49]	NR	65	NR	1/65 (1.8%)	0/55 (0%)	1/10 (10%)
Denmark[50]	NR	163	RIPA then FIPA then CBIA	1/163 (0.6%)	0/NR	1/NR
Denmark[34]	100% WC	51	CBIA	0/51 (0%)	0/NR	0/NR
Finland[51]	100% WC	191	RIPA	3/191 (1.6%)	3/NR	0/NR
Europe and Turkey[52]	96% WC	139	FIPA	8/139 (5.8%)	NR	NR
China[53]	NR	5	CBIA	1/5 (20%)	NR	1/NR
China[54]	NR	23	CBIA	10/23 (43.5%)	NR	NR
China[55]	100% Chinese	128	CBIA	45/128 (35.2%)	39/97 (40.2%)	6/31 (19.4%)
China[56]	100% Chinese	215	CBIA	70/215 (32.6%)	64/NR	6/NR
China[57]	100% Chinese	49	CBIA	11/49 (22.4%)	NR	NR
China[10]	NR	225	CBIA	76/225 (33.8%)	50/168 (29.8%)	26/57 (45.6%)
China[58]	NR	158	CBA	67/158 (42.4%)	58/126 (46.0%)	9/32 (28.1%)
South Korea[59]	100% Korean	42	IIFA	6/42 (14.3%)	4/39 (10.3%)	2/3 (66.7%)
South Korea[60]	NR	37	NR	14/37 (37.8%)	NR	NR

Japan[61]	NR	29	IIFA	1/29 (3.4%) ∮	NR	NR
Japan[62]	100% Japanese	32	CBA	3/32 (9.4%)	0/16 (0%)	3/16 (18.8%)
Japan[63]	100% Japanese	531	IIFA	66/531 (12.4%)	NR	NR

Table 3: Proportion of first episode of unselected optic neuritis cases having serum anti-aquaporin 4 antibodies according to the country of origin listed from West to East starting from the United States of America

* = The ethnicity was not reported for the 110 included subjects but the population from which the subjects came from was reported to be 86% white Caucasian
∮ = Also positive for anti-myelin oligodendrocyte glycoprotein antibodies
AQP4 = Aquaporin 4; CBA = cell-based assay; CBIA = Cell-based immunofluorescence assay; FIPA = fluorescence-based immunoprecipitation assay; IIFA = indirect immunofluorescence assay; NR = Not reported; ONTT = Optic Neuritis Treatment Trial; RIPA = radioimmunoprecipitation assay; USA = United States of America; WC = white Caucasian.

Country	Ethnicity of subjects	Number of subjects	Anti-MOG antibody assay method	Proportion (%) anti-MOG antibody positive amongst all optic neuritis cases	Proportion (%) anti-MOG antibody positive amongst unilateral optic neuritis cases	Proportion (%) anti-MOG antibody positive amongst bilateral simultaneous optic neuritis cases
USA (ONTT cohort)[47]	88.1% WC	177	Live flow cytometry CBA	3/177 (1.7%)	3/177 (1.7%)	N/A
USA[27]	NR*	105	Live flow cytometry CBA	6/105 (5.5%)	1/NR	5/NR
France[49]	NR	65	Live CBA	9/65 (13.8%)	5/55 (9.1%)	4/10 (40.0%)
Denmark[34]	100% WC	51	Live CBA	2/51 (3.9%)	NR	NR
Iran[64]	NR	98	CBA	12/98 (12.2%)	10/95 (10.5%)	2/3 (66.7%)
China[56]	100% Chinese	215	Live CBA	31/215 (14.4%)	NR	NR
China[10]	NR	225	Live CBA	49/225 (21.8%)	34/168 (20.2%)	15/57 (26.3%)
China[58]	NR	158	CBA	31/158 (19.6%)	22/126 (17.7%)	9/32 (28.1%)
Japan[65]	NR	70	CBA	18/70 (25.7%)	NR	NR
Japan[61]	NR	29	CBA	8/29 (27.6%) ∮	NR	NR
Japan[63]	100% Japanese	531	CBA	54/531 (10.2%)	NR	NR

Table 4: Proportion of first episode of unselected optic neuritis cases having serum anti-myelin oligodendrocyte glycoprotein antibodies according to the country of origin listed from West to East starting from the United States of America

* = The ethnicity was not reported for the 110 included subjects but the population from which the subjects came from was reported to be 86% white Caucasian

∮ = One of whom was also positive for anti-aquaporin 4 antibodies

CBA = cell-based assay; MOG = Myelin oligodendrocyte glycoprotein; NR = Not reported; NR* = The ethnicity was not reported for the 110 included subjects but the population from which the subjects came from was reported to be 86% white Caucasian; ONTT = Optic Neuritis Treatment Trial; USA = United States of America; WC = white Caucasian.

Country	No. of cases	Mean or median age (SD/ range) in years	Ethnic mix	Gender mix	Presence of pain	Presence of optic disc swelling	% bilateral at onset	Presenting VA - % of patients	Treatment	Outcome VA - % of patients/eyes after mean/ median F/U time
USA ONTT [14,15,68]	448	31.8 (SD 6.7)	85.3% WC 12.7% AA 1.5% Asian 0.4% Hispanic	77.2% female	92.2%	35.3%	N/A	≥1.0 - 10.5% ≤0.1 - 35.9%	IVMP 250 mg QDS for 3 days then oral prednisone taper for 11 days / or oral prednisone 1 mg/kg for 14 days / or oral placebo	>1.0 - 68.5% ≤0.1 - 3.4% 1 year
France[69]	23	36 (21-63)	NR	82.6% female	74.1%	41.7%	13%	Mean 1.33 logMAR	All except 1 received IVMP (1 g/day for at least 3 days). 21.7% were treated with PLEX	≤0.5 - 31.6% <0.2 - 15.8% Time NR
France[49]	36	33.1 (SD 10.8)	NR	77.8% female	66.7%	13.9%	2.8%	≤0.1 - 41.7%	IVMP 1g/day for 3 days	≥1.0 - 54.5% ≤0.1 - 11.1% 2 months
China[10]	100	31.3 (SD 13.2)	NR	63.0% female	86%	40%	16%	≥0.8 - 5.2% <0.1 - 52.6%	NR	≥0.8 - 72.4% <0.1 - 6.9% 6 months
China[58]	60	38	NR	76.7% female	51.7%	63.3%	23.3%	>0.5 - 2.7% <0.1 - 79.7%	IVMP 1 g/day for 3-5 days, followed by 1 mg/kg oral prednisolone for at least 3 months, based on individual clinician preference and ON subtype	>0.5 - 48.2% <0.1 - 32.5% 31.4 weeks
Japan[63]	410	47.5 (4-87)	100% Japanese	63.7% female	46.4%	46%	NR	≤CF - 22.4%	80% received 1000 mg of steroid pulse therapy for 3 days then 40-60 mg oral prednisolone.	≥0.63 - 56.1% ≤CF - 8.0% Time NR

Table 5 - Studies of presenting features, treatment and outcome for studies of first episode of serum anti-aquaporin 4 and anti-myelin oligodendrocyte antibody negative optic neuritis compared with the results of the Optic Neuritis Treatment Trial according to the country of origin listed from West to East starting from the United States of America

AA = African American; CF = Counting fingers; F/U = Follow up; IVMP = Intravenous methylprednisolone; N/A = Not applicable; NR = Not reported; ON = Optic neuritis; ONTT = Optic Neuritis Treatment Trial; PLEX = Plasma exchange; QDS = Four times per day; SD = Standard deviation; USA = United States of America; VA = Visual acuity; WC = White Caucasian.

Country	No. of cases	Mean or median age (SD/ range) in years	Ethnic mix	Gender mix	Presence of pain	Presence of optic disc swelling	% bilateral at onset	Presenting VA - % of patients	Treatment	Outcome VA - % of patients/eyes after mean/median F/U time
USA[71]	14	46.5 (SD 14.8)	100% WC	71.4% female	94.1%	23.1%	19%	≤0.1 - 45.5%	IVMP with PLEX (in 14.3% of episodes) or IVIG (in 4.8% of episodes) then rituximab in 78.6% (alone or in combination)	≤0.1 - 27% 52.8 months
Argentina[48]	17	31.6 (SD 11.1)	NR	47.1% female	NR	NR	35.3%	≥0.5 - 11.7% ≤0.1 - 76.4%	IVMP 1 g/day for 3 days	≥0.5 - 58.8% ≤0.1 - 29.5% 6 months
France[69]	18	32 (17-54)	NR	94.4% female	85.7%	17.6%	27.8%	Mean 1.41 logMAR	NR	≤0.5 - 22.2% <0.2 - 18.5% Time NR
India[72]	8	30.5 (15.9/16-62)	NR	100% female	NR	NR	50%	Mean 1.85 logMAR	IVMP 1 g/day for 3–5 days with oral steroids taper for 11 days then azathioprine 2.5–3 mg/kg per day	≥1.0 - 12.5% 1 year
Thailand[71]	16	44.4 (SD 21.0)	100% Thai	93.8% female	77.8%	21.1%	10.5%	≤0.1 - 94.7%	IVMP with PLEX (in 10.5% of episodes) then azathioprine in 75.0% and cyclophosphamide in 18.75%	≤0.1 - 52.4% 17.8 months
Thailand[73]	58	39.1 (14.5/18-73)	NR	98.3% female	19%	13.8%	29.3%	≥0.33 - 10.3% <0.1 - 74.1%	IVMP 1g/day for 3-5 days followed by a subsequent tapering dose of oral prednisolone for 6 months and long-term immunosuppressants	≥0.33 - 31.0% <0.1 - 60.3% ≥12 months
Thailand[74]	50	36 (4-84)	100% "Asian"	94.0% female	57.1%	28.5%	16%	≥0.29 - 11.2% <0.1 - 69.8%	IVMP 1g/day (adults) or 30 mg/kg/day (maximum 1g/day) (children) for 3–5 days followed by slowly tapered oral prednisolone	≥0.29 - 66.7% ≤0.1 - 14.3%

									for 2–3 months and immunosuppressive drugs. Adjunctive PLEX therapy in 4 affected eyes	56 days
China[55]	45	34.6 (18-55)	100% Chinese	91.1% female	53.3%	28.9%	13.3%	≥0.5 - 4.0% ≤0.1 - 78.4%	IVMP 1 g/day for 3 days then oral prednisolone tapered over 6 months. 26.7% also received azathioprine and 15.6% mycophenolate	≥0.5 - 45.1% ≤0.1 - 45.1% Time NR
China[10]	76	40.7 (SD 15.3)	NR	92.1% female	75%	32.9%	34.2%	≥0.8 - 1.0% <0.1 - 74.5%	NR	≥0.8 - 19.6% <0.1 - 47.1% 6 months
China[75]	45	35.6 (15.7/8-72)	97.8% Han Chinese	93.3% female	NR	20%	37.8%	<0.1 - 71.1%	IVMP and oral steroids in the acute phase	<0.1 - 46.7% 51.0 months
China[58]	67	36.9 (18-72)	NR	89.6% female	43.3%	32.8%	13.4%	>0.5 - 3.9% <0.1 - 76.3%	IVMP 1 g/day for 3-5 days, followed by 1 mg/kg oral prednisolone for at least 3 months, based on individual clinician preference and ON subtype	>0.5 - 32.2% <0.1 - 47.8% 44.1 weeks
South Korea[59]	6	38.7 (SD 11.5)	100% Korean	83.3% female	NR	NR	33.3%	Mean 3.09 logMAR	Steroid pulse therapy in 100%	≤0.1 - 33.3% 8-32 months
Japan[63]	66	52.5 (13-84)	100% Japanese	83.9% female	52.5%	34.4%	NR	≤CF - 52.5%	89% received 1000 mg of steroid pulse therapy for 3 days then 40-60 mg oral prednisolone. 32% had additional PLEX	≥0.63 - 44.4% ≤CF - 22.2% Time NR

Table 6 - Studies of presenting features, treatment and outcome for studies of first episode of optic neuritis in neuromyelitis optica spectrum disorder according to the country of origin listed from West to East starting from the United States of America

CF = Counting fingers; F/U = Follow up; IVIG = Intravenous immunoglobulin; IVMP = Intravenous methylprednisolone; NR = Not reported; ON = Optic neuritis
PLEX = Plasma exchange; SD = Standard deviation; USA = United States of America; VA = Visual acuity; WC = White Caucasian.

Country	No. of cases	Mean or median age (SD/ range) in years	Ethnic mix	Gender mix	Presence of pain	Presence of optic disc swelling	% bilateral at onset	Presenting VA - % of patients	Treatment	Outcome VA - % of patients/eyes after mean / median F/U time
France[76]	47	37	65% WC	51.1% female	89.4%	70.2%	40.4%	<0.1 - 34.8%	IV steroids 1g/day for 3-10 days in 78.7% of with additional PLEX in 19.2% (2.1% untreated)	≤0.1 - 1.7% 3 months
France[77]	9	39.3 (18.4/17-67)	NR	44.4% female	88.9%	NR	66.7%	<0.1 - 46.7%	88.9% received IV pulse corticosteroid therapy. 55.5% were treated with additional PLEX and 55.5% received immunomodulatory drugs	≥1.0 - 50.0% <0.1 - 5.6% 3.3 years
France[78]	25	35.7 (15-60)	NR	52.0% female	88%	64%	80%	<0.1 - 52.0%	96.0% received 500mg-1g IVMP for 3-10 days with additional PLEX in 16.0% 36.0% continued on maintenance therapy	≥1.0 - 84.0% 6 months
France[49]	9	38.9 (SD 18.0)	NR	33.3% female	100%	77.8%	44.4%	≤0.1 - 77.8%	IVMP 1g/day for 3 days	≥1.0 - 62.5% ≤0.1 - 0% 2 months
France[79]	62	38.1 (16-67)	NR	59.7% female	90.1%	66.2%	41.9%	≤0.1 - 71.0%	All except 2 treated with IVMP	<0.1 - 4.7% 25.4 months
China[10]	49	31.3 (SD 15.3)	NR	55.1% female	85.7%	42.9%	30.6%	≥0.8 - 6.25% <0.1 - 46.9%	NR	≥0.8 - 67.2% <0.1 - 3.1% 6 months
China[75]	20	20.2 (17.4/5-63)	100% Han Chinese	70.0% female	NR	80%	45%	<0.1 - 67.5%	IVMP and oral steroids in the acute phase	<0.1 - 20.0% 29 months
China[58]	31	39.6 (18-63)	NR	64.5% female	64.5%	67.7%	29%	>0.5 - 5.0% <0.1 - 70.0%	IVMP 1 g/day for 3-5 days, followed by 1 mg/kg oral prednisolone for at least 3 months, based on individual clinician preference and ON subtype	>0.5 - 76.0% <0.1 - 14.0% 37.8 weeks

China[80]	23	22 (4-63)	100% Asian	52.2% female	NR	NR	NR	>0.5 - 31.0% ≤0.1 - 59.0%	All cases received IVMP during acute attacks with additional IVIG or PLEX in an unspecified proportion. 47.8% received immunosuppression	>0.5 - 72.7% ≤0.1 - 9.0% 20 months
South Korea[81]	11	45.0 (21.0/15-70)	NR	45.5% female	73%	64%	45.5%	<0.1 - 50.0%	IVMP 250 mg QDS for 3-5 days then tapering oral prednisone at the discretion of the clinician	>0.5 - 100% 42.6 months
Japan[63]	54	47.0 (3-82)	100% Japanese	51.0% female	76.6%	75.6%	NR	≤CF - 25.0%	86% received 1000 mg of steroid pulse therapy for 3 days then 40-60 mg oral prednisolone. One patient (1.4%) had additional PLEX	≥0.63 - 74.4% ≤CF - 5.1% Time NR

Table 7 - Studies of presenting features, treatment and outcome for studies of first episode of myelin oligodendrocyte glycoprotein antibody seropositive optic neuritis according to the country of origin listed from West to East starting from France

CF = Counting fingers; F/U = Follow up; IV = intravenous; IVIG = intravenous immunoglobulin; IVMP = Intravenous methylprednisolone; NR = Not reported; ON = Optic neuritis; PLEX = Plasma exchange; QDS = Four times per day; SD = Standard deviation; VA = Visual acuity; WC = White Caucasian.