

Incidence and Prevalence of NMO in Australia and New Zealand: a population-based, clinical survey

Australia and New Zealand Neuromyelitis Optica (ANZ NMO) Collaboration*

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Abstract

Introduction: Neuromyelitis optica (NMO) is a distinct demyelinating disease of the central nervous system in which a seemingly pathogenic antibody directed against aquaporin-4 (AQP4) can be detected in the majority of cases. It is important to establish the true prevalence of this disease in differing populations in order to better understand potential risk factors and resolve diagnostic difficulties. We have therefore undertaken a population based survey of NMO in Australia and New Zealand.

Methods: Centres managing patients with demyelinating disease of the CNS across Australia and New Zealand reported patients with clinical and laboratory features that were suspicious for NMO. Testing for AQP4 antibodies was undertaken in all suspected cases. From this group, cases were identified who fulfilled the 2015 Wingerchuk diagnostic criteria for NMO. A capture-recapture methodology was used to estimate incidence and prevalence, based on additional laboratory identified cases.

Results: NMO was confirmed in 81/168 (48%) cases referred. Capture-recapture analysis gave an adjusted incidence estimate of 0.37 (95% CI 0.36 – 0.38) per million and a prevalence estimate for NMO of 0.70 (95% CI 0.66 – 0.74) per 100,000. NMO was 3-times more common in the Asian population (1.57 [95% CI 1.36 – 1.77] per 100,000) compared with the remainder of the population (0.57 [95% CI 0.54 – 0.61] per 100,000). The latitudinal gradient evident in multiple sclerosis was not seen.

Discussion: Incidence and prevalence rates of NMO in Australia and New Zealand are comparable with figures from other populations of largely European ancestry. We have found NMO to be more common in the Asian population.

Introduction

Neuromyelitis optica (NMO) is an antibody-mediated autoimmune disease of the central nervous system (CNS) in which the primary target is aquaporin 4 (AQP4), a water channel found in high density on the podocytes of astrocytes, particularly those in close proximity to the blood brain barrier.[1] Pathological studies indicate that while there is demyelination, the fundamental pathology is an astrocytopathy.[2] Earlier difficulties in identifying NMO and distinguishing it from multiple sclerosis were dramatically reduced by the discovery of anti-AQP4 antibodies in 2004.[3] Since the identification of these seemingly specific and pathogenic antibodies,[4] the phenotype of this autoimmune astrocytopathy has broadened[5, 6] and what was once considered to be an extremely rare disorder has been recognised with greater frequency.[7] It has also been noted that whilst in populations of predominantly European ancestry NMO represents perhaps just 1% of CNS demyelinating disease,[8] in Asian populations the relative frequency of NMO and MS is closer to 1:1.[9]

A number of studies have attempted to estimate the population prevalence and incidence of NMO in various parts of the world. However, many of these studies have been clinic-based or based on AQP4 antibody positivity from laboratories. As a result few population-based or clinical surveys of the frequency of NMO exist.[10] Australia and New Zealand have a combined population of approximately 27 million people with predominantly European ancestry and have comprehensive healthcare systems, with a network of adult and paediatric neurologists who have subspecialty interest in demyelinating disease of the CNS. In this setting we have undertaken a population-based survey of NMO, using a clinically-based method of case ascertainment with the aim of estimating the population incidence and

prevalence of NMO. As secondary aims we wished to explore the geographical and ethnic distribution of NMO.

Methods

Case Ascertainment

Possible cases of NMO were identified using a network of 36 adult and paediatric neurologists at 23 clinics specialising in demyelinating diseases across Australia and New Zealand. These centres covered every capital and major city of each state or region, as well as several smaller urban centres. Participating neurologists and paediatric neurologists were requested to notify the coordinating centre in Queensland of all possible cases of neuromyelitis as defined by clinical features highly suggestive of NMO identified in earlier diagnostic criteria,[7] during the period 1 January 2011 to 31 December 2013. These 'high risk' clinical features were defined as 1) optic neuritis that was either severe with poor recovery (residual visual acuity in better eye worse or equal to 6/36), bilateral (simultaneous or sequential within 3 months) or recurrent optic neuritis (more than 2 attacks) as the sole clinical manifestation of demyelinating disease, 2) severe transverse myelitis with a central cord syndrome (symmetrical, motor, sensory and bladder involvement) and poor recovery (residual EDSS less than 5.0) or a longitudinally extensive lesion on magnetic resonance imaging (MRI) of the spinal cord spanning 3 or more vertebral segments or 3) demyelinating disease clinically confined to the optic nerve and spinal cord with at least one of the following: normal or atypical MRI of the brain (fewer than 2 periventricular lesions[11]), negative oligoclonal bands in cerebrospinal fluid, raised CSF protein or a CSF pleiocytosis (more than 10 cells per μ l). Informed, written consent was obtained for all cases and

institutional human research ethics committee approval was obtained for all participating sites.

To facilitate a capture-recapture methodology, the four laboratories in Australia that offer routine AQP4-Ab screening provided details of positive cases detected in their laboratories for the same time period. Details in these cases included date of birth, initials, age, gender, state/country and ethnicity [Asian or Other]) thereby ensuring the avoidance of double counting and facilitating a whole of population analysis by age, gender, region and ethnicity.

Case Definition

Demographic details (age, gender and ethnicity), relapse history, findings on clinical examination and results of CSF analysis and any prior AQP4-Ab testing were collected in all cases. Serum samples were obtained in all cases and tested for AQP4-Ab using immunofluorescence staining techniques on mouse, rat or monkey brain tissue and rat or mouse kidney sections. A subset of samples was also tested using an ELISA kit, as well as M23 AQP4 transfected HEK cells in a fixed cell assay (Euroimmun™, Germany) and a live cell based assay.[12] MRI of brain, orbits and spinal cord were obtained where available. Cases were defined as having NMO if they met the 2015 Wingerchuk criteria.[13] Numbers of cases are presented as n/N (%).

Estimation of incidence and prevalence

Crude incidence rates with 95% confidence intervals were calculated, using the normal approximation to the binomial distribution, from the mean number of cases with disease onset occurring from 2009 to 2012 inclusive. Because of the

inevitable lag between symptom onset and presentation and clinical assessment meaning that new cases would typically identified and referred to the study sometime after the onset of their symptoms, incident cases for the collection year 2013 were not included. Crude point prevalence rates were calculated for the prevalence date of 1 July 2013. To be included in the prevalence estimate cases were required to have disease onset on or before 1 July 2013 and be alive on this date. Gender and age-adjustment was performed using the WHO Standard World Population Distribution for 2005 to 2025.[14]

The Lincoln-Peterson capture-recapture method[15] was used to adjust prevalence and incidence rates in light of laboratory identified cases that had been missed in the clinical survey. Standard methods were used to estimate a 95% confidence interval for this adjusted prevalence rate.[16] All analyses were conducted on a state and country basis, to allow for regional variations in referral practice, before being combined. Prevalence rates were also estimated for cases with Asian ancestry separately.

Population estimates for Australian states and New Zealand were obtained from the Australian Bureau of Statistics and Statistics New Zealand websites.[17, 18] For incidence, population estimates for 2011 were used. For prevalence, population estimates for 2013 were used. Latitudinal variation in prevalence was analysed using the latitude of the capital city for each state or country.[19]

Results

Incidence and prevalence of NMO

A total of 177 cases of suspected NMO were referred to the study centre. Of these 9/177 (5) were excluded (no serum sample received in 3, inclusion criteria not met in 3, incomplete clinical data in 2 and alternate diagnosis in 1). NMO was confirmed in 81/168 (48) cases and 73/81 (90) were seropositive. An additional 70 AQP4 positive cases were identified from the laboratory survey giving an estimated total of 151 cases of NMO. There were 34 incident cases over the period 2010 to 2012, giving a crude incidence of 0.33 (95% CI 0.11 – 0.55) per million. Two cases died prior to the prevalence date and 2 cases had disease onset after the prevalence date leaving 147 prevalent cases and giving a crude point prevalence of 0.53 (95% CI 0.45 – 0.62) per 100,000. Standardising to the World Health Organisation 2005-2025 world population gave a gender and age-adjusted prevalence figure of 0.44 (95% CI 0.36 – 0.52) per 100,000. There were 126/147 (86) female cases, giving a female to male ratio of 6:1. The frequency distribution by age is shown in Figure 1. The peak prevalence age range for women was 40 – 59 years and for men was 60 – 69 years.

Capture-recapture analysis and lifetime risk of NMO

A total of 47 cases were recaptured in the laboratory survey that had already been 'marked' in the clinical survey. Capture-recapture analysis gave an adjusted incidence estimate of 0.37 (95% CI 0.36 – 0.38) per million and gave a total number of NMO cases of 206 with a prevalence estimate of 0.70 (95% CI 0.66 – 0.74) per 100,000. The prevalence of NMO in the population of Australia and New Zealand with Asian ancestry was 1.57 (95% CI 1.36 – 1.77) per 100,000 compared with 0.57 (95% CI 0.54 – 0.61) per 100,000 in the remainder of the population. The cumulative age of onset for the clinical survey cases was used to calculate the lifetime risk of developing NMO which was 1.26 (95% CI 1.13 – 1.39).

Latitudinal variation in NMO prevalence

The prevalence estimates by region are illustrated in Figure 2 and show no increase in prevalence with increasing latitude. In fact there is a reverse relationship which is statistically significant ($\chi^2_{\text{trend}} = 12.88$; $p=0.0003$). Exclusion of cases and state populations with Asian ancestry did not significantly alter this finding.

Discussion

This is the first incidence and prevalence survey of NMO in the Oceania region. We have utilised a unique clinical survey method combined with a laboratory-based capture-recapture methodology to estimate the incidence and prevalence of NMO in Australia and New Zealand and have results that are similar to those previously recorded for both European and Asian populations. The estimates of incidence and prevalence reported here are at the lower end of previous study results (Table 1). The overall estimated number of cases of NMO (206) represents approximately 1% of the 26,600 people with multiple sclerosis estimated to be living in Australia[20] and New Zealand.[21] This is a similar proportion to that seen in other European populations. The increased frequency of NMO in women is consistent with previous studies. We have demonstrated a higher prevalence of NMO in people with Asian ancestry (3-fold increase compared the remaining predominantly European ancestry population) in a survey using the same methodology across a single geographical region.

Table 1

Study [ref]	Population	Incidence	(95% CI)	Prevalence	(95% CI)
Cabrera-Gomez et al 2009 [22]	Cuba	0.44	(0.3 - 0.62)	0.43	(0.29 - 0.61)
Asgari et al 2011 [23]	Denmark	4	(3 - 5.4)	4.41	(3.1 - 5.7)
Cossburn et al 2012 [24]	Wales			1.96	(1.22 - 2.97)
Jacob et al 2013 [25]	Merseyside	0.8	(0.3 - 1.6)	0.72	
Etemadifar et al 2014 [26]	Iran			1.95	(1.62 - 2.23)
Kashopazha et al 2015 [27]	Iran			0.8	(0.54 - 1.06)
Flanagan et al 2016 [28]*	Olmstead	0.7	(0 -2.1)	3.9	(0.8 - 7.1)
Present Study	ANZ	0.37	(0.36 - 0.38)	0.7	(0.66 - 0.74)

Results are as presented in original papers. ANZ = Australia and New Zealand

* Age and gender-adjusted figures

The present data do not support a latitudinal gradient in NMO as compared with MS for this region.[29, 30] In fact the data suggest a possible weak inverse relationship, with prevalence increasing at lower latitudes. This does not appear to be explained by regional variations in the proportion with Asian ancestry in each region as the trend remained when these populations were removed. Another possible explanation could be ease of access to serological testing, as the two states with the highest prevalence of NMO have the two laboratories with the highest throughput of AQP4 antibody testing. The proportions of new cases identified through the laboratory survey certainly suggest that this may have been a factor with the two most distant regions (South Australia/Northern Territory) and New Zealand having the lowest proportions of cases detected through the laboratory survey. We have demonstrated an increased frequency of NMO in women compared to men consistent with previous studies (Table 2).

Table 2

Author	Population	Inclusion Criteria	N	Female (%)	Male (%)	Ratio (F:M)
<i>Asian</i>						
Nagaishi et al 2011 [31]	Japan	AQP4-Ab positive	583	533 (91)	50 (9)	10.7:1
Barhate et al 2014 [32]	India	2006 Wingerchuk	44	39 (89)	5 (11)	7.8:1
Pandit & Kundapur 2014 [33]	India	2006/2007 Wingerchuk	11	6 (55)	5 (45)	1.2:1
Yin et al 2015 [34]	China	2006 Wingerchuk plus ^a	108	92 (85)	16 (15)	5.8:1
<i>Black</i>						
Flanagan et al 2016 [28]	US/Martinique	AQP4-Ab positive	45	40 (89)	5 (11)	8:1
Daoudi & Bouzar 2016 [35]	Algeria	2015 Wingerchuk	8	6 (75)	2 (25)	3:1
<i>Caucasian</i>						
Rivera et al 2008 [36]	Mexico	1999 Wingerchuk	34	24 (71)	10 (29)	2.4:1
Cabrera-Gomez et al 2009 [22]	Cuba	1999 Wingerchuk	58	51 (88)	7 (12)	7.3:1
Asgari et al 2011 [23]	Denmark	2006 Wingerchuk	42	31 (74)	11 (26)	2.8:1
Collongues et al 2011 [37]	France	2006 Wingerchuk	155	108 (70)	47 (30)	2.3:1
Cosburn et al 2012 [24]	Wales	2007 Wingerchuk	14	12 (86)	2 (14)	6:1
Aboul-Enein et al 2013 [38]	Austria	AQP4-Ab positive	71	62 (87)	9 (13)	6.9:1
Jacob et al 2013 [25]	England	2006 Wingerchuk	8	7 (88)	1 (13)	7:1
Etemadifar et al 2014 [26]	Iran	2006 Wingerchuk	95	66 (69)	29 (31)	2.3:1
Kashipazha et al 2015 [27]	Iran	Unique ^b	36	30 (83)	6 (17)	5:1
Chitnis et al 2016 [39]	US ^c	2006 Wingerchuk plus ^d	38	26 (68)	12 (32)	2.2:1
Sepulveda et al 2016 [40]	Spain	2006 Wingerchuk	181	157 (87)	24 (13)	6.5:1
Kleiter et al 2016 [41]	Germany	2006 Wingerchuk plus ^a	186	152 (82)	34 (18)	4.5:1
Present Study	ANZ	2015 Wingerchuk	147	126 (86)	21 (14)	6:1
Combined			1864	1568 (84)	296 (16)	5.3:1

^a additional criteria included AQP4-Ab positive high risk syndromes; ^b additional criteria included those suggested by Lana-Peixoto & Callegaro 2012 [42] ^c paediatric population; ^d additional criteria included expert panel review

2006 Wingerchuk criteria [7]

2007 Wingerchuk criteria [5]

2015 Wingerchuk criteria [13]

In conclusion, the Australia and New Zealand region has incidence and prevalence estimates for NMO which are within the ranges seen in other populations around the world, with the possible exception of populations with African ancestry.[28] The prevalence of NMO is higher in people with Asian ancestry compared with the remaining predominantly European ancestry population of Australia and New Zealand and NMO does not share the latitudinal gradient seen with MS across this region. It therefore seems unlikely that exposure to sunlight and relative vitamin D deficiency play any significant role in NMO susceptibility.

Figure Legends

Figure 1

Gender and age distribution of NMO in Australia and New Zealand.

Figure 2

Latitudinal variation in prevalence of NMO across Australia and New Zealand.

Table 1

Incidence and prevalence of NMO in populations of Caucasian ancestry

Table 2

Female:Male ratios in NMO cohorts

Conflicts of Interest

None for all authors

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