The clinical profile of NMOSD in Australia and New Zealand

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ABSTRACT

Neuromyelitis optica spectrum disorders (NMOSD) are an inflammation of the central nervous system associated with autoantibodies to aquaporin-4. We have undertaken a clinic-based survey of NMOSD in the Australia and New Zealand populations with the aim of characterising the clinical features and establishing the value of recently revised diagnostic criteria. Cases of possible NMOSD and age and sex-matched controls with multiple sclerosis (MS) were referred from centres across Australia and New Zealand. Cases were classified as NMOSD if they met the 2015 IPND criteria and remained as suspected NMOSD if they did not. Clinical and paraclinical data were compared across the three groups. NMOSD was confirmed in 75 cases and 89 had suspected NMOSD. There were 101 controls with MS. Age at onset, relapse rates and EDSS scores were significantly higher in NMOSD than in MS. Lesions and symptoms referable to the optic nerve were more common in NMOSD whereas brainstem, cerebellar and cerebral lesions were more common in MS. Longitudinally extensive spinal cord lesions were seen in 48/71 (68%) of cases with NMOSD. Elevations of CSF white cell count and protein were more common in NMOSD. We have confirmed a clinical pattern of NMOSD that has been seen in several geographical regions. We have demonstrated the clinical utility of the current diagnostic criteria. Distinct patterns of disease are evident in NMOSD and MS, but there remains a large number of patients with NMOSD-like features who do not meet the current diagnostic criteria for NMOSD and remain a diagnostic challenge.

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) encompasses clinical presentations associated with antibodies to aquaporin-4 (AQP4), a water channel expressed on astrocytes [1]. Without treatment NMOSD is frequently a disabling, sometimes fatal condition, with high annualised relapse rates and poor recovery after each attack. Studies suggest that the treatment response in NMOSD is quite distinct to that seen in multiple sclerosis (MS) with NMOSD being highly steroid responsive and to some extent steroid dependent [2]. Acute treatment with plasma exchange appears to be particularly helpful in NMOSD. Several immunomodulatory treatments for MS (β-interferon, fingolimod and natalizumab) may worsen NMOSD [3-5] and alemtuzumab has shown no discernible benefit in a small number of cases of NMOSD [6]. NMOSD appears to be responsive to immunosuppressive therapy and anti-B-cell therapies (e.g. rituximab, inebilizumab) [7,8]. More recently treatment efficacy with anti-IL6 receptor (tocilizumab) [9] and anti-complement component 5 (eculizumab) [10] monoclonal antibodies has been demonstrated. Due to this prognostic and therapeutic divergence between NMOSD and MS it is important to recognise NMOSD early.

Since the discovery of pathogenic antibodies that are present in the majority of patients with NMSOD, the disease has been more clearly defined and the clinical phenotype has expanded to include cases of area postrema dysfunction, brainstem disease, hypothalamic dysfunction, encephalopathic presentations and cerebral lesions in addition to the originally described optic neuritis and longitudinally extensive spinal cord disease [11]. The most recent diagnostic criteria for NMOSD

emphasise the value of positive AQP4 antibodies in patients with a core clinical presentation, but also accommodate cases where AQP4 antibodies are negative or unknown [11]. There are few studies of cohorts of patients with NMOSD as defined by the 2015 International Panel for NMO Diagnosis (IPND) diagnostic criteria [11]. We have therefore undertaken a clinical survey of NMOSD across 23 central nervous system (CNS) demyelination clinics in Australia and New Zealand with the aim of outlining the clinical profile of the disease in this region and evaluating the new diagnostic criteria. We have also compared the NMOSD patients with a cohort of contemporaneously recruited patients with classical MS and the cases of suspected NMOSD who did not meet the 2015 IPND criteria.

Methods

Data Collection

Cases of “possible NMOSD” were identified by clinicians experienced in the diagnosis of inflammatory CNS disease at 23 adult and paediatric clinics covering the major urban centres of Australia and New Zealand. Possible NMOSD was determined using the clinical and para-clinical features of NMOSD as defined in the 2006 Wingerchuk criteria as being features associated with a high risk for NMOSD (Table 1) [12]. Age and sex-matched cases with MS were also recruited from the same locations. Cases were collected between 1 January 2011 and 31 December 2013. Demographic and clinical features were collected for all cases and controls using a questionnaire designed to provide information regarding the patient’s age, gender, ethnic ancestry, age at onset, relapse profile, associated medical conditions,

past history of glandular fever, smoking history, family history of demyelinating disease, medication history, disease course and current symptoms. Symptom severity was rated using a self-reported four-point scale of 0 = symptom not present; 1 = intermittent or mild symptoms; 2 = persistent symptoms that are moderate in severity; and 3 = severe symptoms that significantly impact activities of daily living. Expanded disability status scale (EDSS) scoring was undertaken by a neurologist experienced in the assessment of demyelinating disease was used to assess disability. Cases were defined retrospectively as “NMOSD” if they met the 2015 IPND criteria (incorporating AQP4 antibody results) [11], “suspected NMOSD” if they were referred as possible NMOSD but did not meet these criteria and “MS” if they were referred as MS, met the 2010 McDonald criteria [13] and were seronegative for AQP4 antibodies. Institutional ethics approval for this study was obtained for all participating centres and all patients gave written, informed consent.

Paraclinical Information

Where available the results of cerebrospinal fluid (CSF) analysis, visual evoked potentials (VEP) and prior laboratory and radiological screening for potential NMOSD mimics and associated autoimmune disease were also recorded. DICOM formatted files of magnetic resonance (MR) imaging of the brain and spine were obtained wherever possible and downloaded to a central reading centre using eFilm® software (IBM Watson Health®, US). Images were reviewed using RadiForce® MX270W high resolution screens (EIZO®, California USA). MR images were reviewed by a single blinded assessor with access available for review by a second blinded assessor in cases of uncertainty. Final decisions were made by consensus.

Serological Testing

Testing for AQP4 antibodies was performed using standard immunofluorescence techniques in all cases and in a subset using a combination of ELISA and cell-based assays for AQP-4 as previously described [14]. All testing was performed blind to the clinical status of the patient.

Statistical Analysis

Frequencies are expressed as n/N (%) and continuous data are presented as median (range) if not normally distributed or mean (SD) if normally distributed. Simple comparisons have been made using appropriate parametric or non-parametric tests for categorical and continuous data. As comparisons were purely exploratory, no correction for multiple testing has been undertaken.

RESULTS

Diagnostic characterization

In total, 296 patients were recruited for inclusion in the study. Of these 179 had possible NMOSD and 117 had MS. Of the NMOSD cases 15/179 (8%) were excluded because of insufficient clinical data (9), study inclusion criteria not met (3), no serum sample available (1), withdawal from study (1) or were given an alternative diagnosis (1 - Leber’s hereditary optic neuropathy). Of the remaining 164 cases,

75/164 (46%) met the 2015 IPND criteria for a diagnosis of NMOSD (68/75 [91%] were AQP4 seropositive) [11], leaving 89 cases with suspected NMOSD. Of the MS controls 16/117 (14%) were excluded, leaving 101 controls. Reasons for exclusion in this group were insufficient clinical data (6) and no serum sample (10). All of the suspected NMOSD cases and MS controls were negative for AQP4 antibodies. The final distribution of cases and MS controls is summarised in Figure 1. MR imaging of the brain was available for 255/265 (96%) and of the spine in 239/265 (90%) cases and controls. There were only 4 instances where lack of appropriate imaging may have resulted in failure for a possible NMOSD case to be catagorised as seronegative NMOSD.

Demographic and Clinical Features

The principal demographic and clinical features of NMOSD cases, suspected NMOSD and MS controls are shown in Table 2. There was no statistically significant difference in the current age and gender ratio for NMOSD and MS, indicating that the matching of MS controls to cases was successful. Median age of onset was higher in NMOSD than in MS ($p=0.001$) and correspondingly disease duration was shorter ($p<0.001$). The distribution of age of onset in the three groups is shown in Figure 2 which shows a flattened distribution and extended tail in the higher age ranges for NMOSD. Onset prior to the age of 10 years was not seen in this NMOSD cohort.

Mean annualised relapse rates and median EDSS at last assessment were both higher in NMOSD than in MS, despite the shorter disease duration. The distribution of EDSS scores is illustrated in Figure 3. A greater relative frequency of EDSS

scores of 4.0 and 6.0-6.5 was apparent for the NMOSD group. Clinical course was not significantly different between the groups, but as has been previously noted a secondary progressive course was rare in NMOSD (2%) and primary progressive disease was not seen [15]. There was no difference in the frequency of relapse types, reflecting the considerable overlap between NMOSD and MS. However, as has been previously noted there was a trend to more frequent episodes of optic neuritis and transverse myelitis in NMOSD and more brainstem and other relapse types in MS (Table 2). Initial MR imaging of the brain was more likely to be normal (not meeting Paty criteria) [16] in NMOSD compared to MS, but this was only the case in 17% of cases (Table 2). Longitudinally extensive spinal cord lesions were seen in 48/71 (68%) cases with NMOSD and 1/89 (1%) in MS ($p<0.001$). The longitudinally extensive spinal cord lesion seen in the MS case had the appearance of coalesced short segment lesions, but was included as it met our definition of continuous central cord lesion extending over 3 or more vertebral segments and was read as such by our blinded MR imaging readers. There were no significant differences in clinical features observed between seropositive and seronegative NMOSD cases (Table 3), but as has been previously reported there was a trend towards older age of onset and a higher frequency of longitudinally extensive spinal cord lesions in the antibody positive group [17].

Symptom severity (none, mild, moderate or severe) at the time of assessment is shown in Figure 4 and indicates that a relatively greater burden of disease in NMOSD was seen in the visual, sensory and motor (particularly lower limb) domains. Brainstem symptoms were more common in MS but were not frequently seen in any group. Complaints of fatigue and cognitive symptoms were similar in the three

groups. The profile of visual acuities is shown in Figure 5. Visual acuities were 6/12 or worse in 31% of eyes in NMOSD and 20% in MS, and counting fingers only (CFO) or worse in 11% of eyes in NMMOSD and 0.6% in MS, despite a shorter disease duration in NMOSD. Suspected NMOSD fell between these two extremes with 25% of eyes 6/12 or worse and 2% CFO or worse.

Relapse Data

A total of 960 relapses were documented across all three groups over a total of 2015 patient-years. The pattern of relapses in the three groups is shown in Table 4. As has been previously noted, episodes of optic neuritis were more common in NMOSD ($p<0.001$) while brainstem/cerebellar ($p<0.001$) and cerebral relapses ($p=0.009$) were more common in MS [18]. Suspected NMOSD had a relapse profile that resembles NMOSD more than MS, reflecting the recruitment criteria. Relapses in NMOSD were more likely to be treated with intravenous methylprednisolone than relapses in MS ($p<0.001$), possibly reflecting greater relapse symptom severity in NMOSD.

The types of relapse encountered at first presentation for cases with NMOSD are given in Table 5. Initial presentations with transverse myelitis were the most common (44%), followed by optic neuritis (38%). Simultaneous optic neuritis and transverse myelitis was only seen in 2/75 (2%) of initial presentations of NMOSD. Area postrema syndrome was the initial presentation in 7/75 (9%).

CSF and VEP Results

Results of CSF analysis are summarised in Figure 6. CSF white cell count and protein levels were higher in NMOSD compared to MS ($p<0.001$), with suspected NMOSD falling in between. Evidence of local synthesis of oligoclonal bands in CSF was more common in MS than in NMOSD or suspected NMOSD and systemic synthesis of oligoclonal bands was seen in a small proportion of NMOSD and suspected NMOSD cases. P100 latency on VEP was significantly longer in MS compared to NMOSD and evidence of bilateral delay was more common in MS than in NMOSD (Figure 7).

Co-occurrence of autoimmune disease

The frequency of co-occurring autoimmune diseases is shown in Table 6. Other autoimmune diseases were more commonly seen in NMOSD than in MS or suspected NMOSD, but these differences were not statistically significant. Although the numbers are small they do suggest a specific association for NMOSD with systemic lupus erythematosus and Sjögren's syndrome and for MS with psoriasis and similar specific associations have been noted previously [19-21].

Discussion

This comprehensive clinical survey of NMOSD across Australia and New Zealand using the most recent diagnostic criteria included 39% of the estimated 193 cases of NMOSD identified in our recent prevalence study [22]. This is therefore likely to be a representative sample. This cohort was identified on the basis of clinical features

previously described as being predictive of NMOSD thereby removing the potential bias of identifying cases through seropositive status alone. This methodology increased the likelihood of identifying seronegative cases. It is noteworthy that there were a large number of suspected cases of NMOSD referred (n=89) with at least one typical NMO feature that did not meet the new diagnostic criteria for NMOSD and all were negative for AQP4 antibodies.

The clinical features observed in this NMOSD cohort are similar to those previously described in other populations from a variety of geographical locations [23-26]. As with other studies performed using the 2015 IPND diagnostic criteria from NMOSD [18,25] the proportion of seropositive cases was high at 91% compared to studies using earlier criteria (27 – 88%) [27,28]. Noting that any criteria that include the AQP4 antibody test as a key component of disease classification will result in high sensitivity for the antibody, the high sensitivity noted in studies using the 2015 IPND criteria suggests that the new diagnostic criteria are appropriately permitting only seronegative cases with two typical presentations and supportive paraclinical features to be included as NMOSD.

As with previous studies [29,18,30] this cohort demonstrates an older age of onset, higher relapse rates, higher EDSS scores, higher CSF white cell counts and protein levels, lower frequency of oligoclonal bands in CSF, less delayed P100 latency on VEP and a higher frequency of co-occurring autoimmune diseases in NMOSD compared to MS. For some clinical features (age at onset, annualized relapse rate, EDSS, CSF white cell count, CSF protein, VEP results) suspected NMOSD cases were intermediate between NMOSD and MS but others were closer to NMSOD

(frequency of oligoclonal bands). The profile of symptoms and relapse locations, with optic neuritis being more common in NMOSD and brainstem, cerebellar and cerebral lesions being more common in MS, is not surprising and is consistent with prior studies [29,18,30]. The frequency of longitudinally extensive spinal cord lesions was most common in NMOSD and was a little lower in suspected NMOSD. Initial MR imaging of the brain was most likely to be normal in cases of suspected NMOSD. These conflicting patterns for cases of suspected NMOSD suggests that they constitute an admixture of pathologies.

The numbers of seronegative NMOSD in the present study were too small to provide statistically significant differences in comparison to seropositive cases. Other studies from the pre-2015 IPND diagnostic criteria, have suggested a number of differences between seronegative and seropositive cases of NMOSD [31].

Strengths of the present study are that we have used the 2015 IPND diagnostic criteria to define cases of NMOSD and that cases have been identified from across Australia and New Zealand using clinical features only to identify potential cases. One drawback in this approach is that only clinical features identified in the 2006 Wingerchuk criteria, which were the criteria at the time of participant recruitment, were used to identify cases and therefore the more recently identified typical presentations of NMOSD (area postrema, acute brainstem, diencephalic and cerebral syndromes) may be under-represented. However, the frequency of area postrema syndrome as a first relapse in our cohort (9%) was similar to that identified in a recently reported figure from a large international database (7.1 – 10.3%) [32].

In summary, this clinically ascertained cohort of NMOSD patients confirms a clinical profile of disease that is consistent with other studies and has been replicated across many geographical locations. New diagnostic criteria are both sensitive and specific for NMOSD and therefore represent a practical way to ascertain cases for clinical studies and will assist diagnosis in routine clinical practice. Distinctly different profiles of clinical features between NMOSD and MS are of considerable assistance in identifying potential cases, but a significant number of cases with NMOSD-like features are antibody negative and do not meet current clinical criteria for a diagnosis of NMOSD, indicating that there is a persistent grey-zone between NMOSD and MS.

Figure Legends

Figure 1

Distribution of cases and controls as defined by diagnostic criteria used in this study.

NMOSD = neuromyelitis optica spectrum disorders

MS = multiple sclerosis

AQP4 = aquaporin-4 antibodies

+ve = positive

-ve = negative

Figure 2

Age at onset distribution of NMOSD cases, suspected NMOSD and MS controls expressed as relative frequency (percentage) within each diagnostic group.

NMOSD = neuromyelitis optica spectrum disorders

Susp NMOSD = suspected NMOSD

MS = multiple sclerosis

Figure 3

Distribution of EDSS scores at last assessment for NMOSD cases, suspected NMOSD and MS controls expressed as relative frequency (percentage) within each diagnostic group.

NMOSD = neuromyelitis optica spectrum disorders

Susp NMOSD = suspected NMOSD

MS = multiple sclerosis

Figure 4

Symptom severity for NMOSD cases, suspected NMOSD and MS controls expressed as relative frequency (percentage) within each symptom cluster for each clinical group.

NMOSD = neuromyelitis optica spectrum disorders

Susp NMOSD = suspected NMOSD

MS = multiple sclerosis

Figure 5

Visual acuity measurements in NMOSD cases, suspected NMOSD and MS controls expressed as relative frequency (percentage) within each clinical group. Visual acuities recorded according to metric Snellen chart for individual eyes. Number of eyes examined: NMOSD = 136, Susp NMOSD = 164; MS = 154.

NMOSD = neuromyelitis optica spectrum disorders

Susp NMOSD = suspected NMOSD

MS = multiple sclerosis

NPL = no perception of light

LPO = light perception only

HMO = hand movements only

CFO = counting fingers only

Figure 6

Summary of CSF examination in NMOSD cases, suspected NMOSD and MS controls showing (A) box and whisker plot of CSF white cell counts (cells per mm^3), (B) box and whisker plot of CSF protein (g/L) and (C) bar chart of frequency

(percentage) of local, systemic, negative or unknown oligoclonal bands results. Numbers (N) of examinations are indicated above each chart. Box and whisker plots shows median (solid bar), interquartile range (boxes) and range (whiskers).

NMOSD = neuromyelitis spectrum disorders

Susp NMOSD = suspected NMOSD

MS = multiple sclerosis

CSF = cerebrospinal fluid

Figure 7

Summary of VEP results for NMOSD cases, suspected NMOSD and MS controls showing (A) box and whisker plot of VEP P100 latency (ms) and (B) bar chart of relative frequency (percentage) of bilateral delay, unilateral delay or normal VEP within each clinical group. Numbers (N) of examinations are indicated above each chart. Box and whisker plot shows median (solid bar), interquartile range (boxes) and range (whiskers).

NMOSD = neuromyelitis optica spectrum disorders

Susp NMOSD = suspected NMOSD

MS = multiple sclerosis

VEP = visual evoked potential

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