Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan

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Neuromyelitis optica and neuromyelitis optica spectrum disorders have been recently associated with the disease-specific autoantibody aquaporin-4, thought to be pathogenic. Identifying this antibody has allowed the clinical phenotype to be broadened. It is clear that some patients with similar clinical features do not have this antibody and may have a different condition with different outcomes and prognosis. Previous clinical neuromyelitis optica and neuromyelitis optica spectrum disorder studies have included such patients. We investigated clinical outcomes and prognostic characteristics of 106 aquaporin-4 antibody-seropositive patients from the UK and Japan. We looked at predictors of disability outcomes, namely visual disability (permanent bilateral visual loss with visual acuity of \( \leq 6/36 \) in the best eye), motor disability (permanent inability to walk further than 100 m unaided), wheelchair dependence and mortality. Data were collected largely retrospectively through review of case records. After median disease duration of 75 months, 18% had developed permanent bilateral visual disability, 34% permanent motor disability, 23% had become wheelchair dependent and 9% had died. Age at disease onset appeared to be an important predictor of disability type. Young-onset patients in the UK, but not the Japanese cohort, commonly presenting with optic neuritis, had a high risk of visual disability while older patients in both cohorts had a high risk of motor disability, regardless of their onset symptom. Genetic factors also appeared important. The UK cohort seemed to have more severe disease than the Japanese cohort, with more severe onset attacks, a higher relapse frequency and greater disability at follow-up, despite earlier immunosuppression. Moreover, within the UK cohort, there were important differences between ethnic groups, with Afro-Caribbean patients having a younger age at disease onset, more brain and multifocal attacks and higher likelihood of visual disability than Caucasian patients. Thus, age at disease onset and genetic factors are both likely to be important in determining clinical outcomes in aquaporin-4 disease. This has important implications for interpreting clinical neuromyelitis optica and...
neuromyelitis optica spectrum disorder studies, since clinical features and outcomes appear not to be generic across populations and may need to be tailored to individual groups. These factors need to be explored further in future prospective neuromyelitis optica and neuromyelitis optica spectrum disorder studies.

Keywords: neuromyelitis optica; NMO; NMO spectrum disorder; aquaporin-4; AQP4; long-term disability; prognosis; outcomes

Abbreviations: AQP4 = aquaporin-4; LETM = longitudinally extensive transverse myelitis; NMO = neuromyelitis optica

Introduction

Neuromyelitis optica (NMO) is an autoimmune inflammatory disorder of the CNS characterized by attacks of predominantly optic neuritis and/or longitudinally extensive transverse myelitis (LETM). Attacks tend to be severe and recurrent, often with incomplete recovery and morbidity and mortality are substantial. Disability is attack related and early recognition and initiation of immunosuppressive treatment to prevent further relapses is essential.

Until recently, NMO was considered a severe form of multiple sclerosis in Japan and referred to as optico-spinal multiple sclerosis, and although recognized as a distinct disease in Western countries, was often misdiagnosed as relapsing-remitting multiple sclerosis, and although recognized as a distinct disease in Western countries, Japan and referred to as optico-spinal multiple sclerosis in Japan and referred to as optico-spinal multiple sclerosis in Japan. AQP4-mediated NMO/NMO spectrum disorder. Only four previous studies (Bizzoco et al., 2009; Cabrera-Gomez et al., 2009a; Cabrera-Gomez et al., 2009b; Adoni et al., 2010; Cabrera-Gomez et al., 2009a, b; Adoni et al., 2010; Collongues et al., 2010; Sahraian et al., 2010, Akman-Demir et al., 2011). Additionally, some excluded patients with clinical or radiological evidence of brain disease (Papais-Alvarenga et al., 2002), those with monophasic disease (Bichuetti et al., 2009; Cabrera et al., 2009; Cabrera-Gomez et al., 2009; Adoni et al., 2010; Cabrera-Gomez et al., 2009a, b; Cabrera-Gomez et al., 2009a, b; Adoni et al., 2010; Collongues et al., 2010; Sahraian et al., 2010, Akman-Demir et al., 2011) and thus may not have provided representative information on the disease characteristics and clinical course of AQP4-mediated NMO/NMO spectrum disorder. Only four previous studies (Bizzoco et al., 2009; Adoni et al., 2010; Akman-Demir et al., 2011; Nagaishi et al., 2011) have published data on a cohort of only AQP4 antibody-seropositive patients with NMO/NMO spectrum disorder, with only one of these (Nagaishi et al., 2011) including all phenotypes. While a few studies have assessed prognostic markers (Wingerchuk et al., 2003; Ghezzi et al., 2004; Bichuetti et al., 2009; Cabrera et al., 2009; Collongues et al., 2010) and disability outcomes (Papais-Alvarenga et al., 2002; Merle et al., 2007; Rivera et al., 2008; Bichuetti et al., 2009; Cabrera et al., 2009; Collongues et al., 2010; Sahraian et al., 2010) in NMO/NMO spectrum disorder, these studies were either performed before the availability of AQP4 antibody testing or grouped together AQP4-positive and -negative patients. There have been no published studies to date looking at disability outcomes and prognostic markers in AQP4 antibody-positive NMO/NMO spectrum disorder.

Here, we describe and compare the clinical outcomes and early long-term prognostic characteristics of 106 AQP4 antibody-seropositive patients with NMO/NMO spectrum disorder from the UK and Japan.
Materials and methods

Case definition

We included 106 consecutively identified patients followed at three tertiary centres for NMO: (i) the John Radcliffe Hospital, Oxford, UK; (ii) The Walton Centre, Liverpool, UK; and (iii) Tohoku University Hospital, Sendai, Japan. The patients included were identified following the introduction of the AQP4 assay at the Oxford and Sendai laboratories in 2006. All patients were seen in a specialist NMO clinic or as inpatients at one of the three centres up to September 2010. All patients had tested positive for AQP4 antibodies in either the Oxford or the Sendai laboratories using a cell-based assay as described previously (Takahashi et al., 2007; Waters et al., 2008). Although differing slightly in their methodologies—the Japanese assay is based on the stable expression of the M1 isoform of human AQP4, while the UK assay is based on the transient expression of the M23 isoform of human AQP4—both assays demonstrate high sensitivity and 100% specificity (Takahashi et al., 2007; Waters et al., 2008, 2012) for NMO spectrum disorder. All patients tested positive for AQP4 antibodies on their earliest available sample. No AQP4 antibody-seropositive patients with NMO/NMO spectrum disorder seen at any of the centres within the stated study period were excluded from the study.

The following anonymized data were collated from the UK and Japanese cohorts: age at disease onset, gender, ethnicity, disease duration, date of commencing prophylactic immunosuppressive therapy, onset symptom, onset severity (severe attack defined as unable to walk at nadir for spinal attack and visual acuity 6/60 or worse in affected eye at nadir for optic neuritis attack), relapse type and frequency, time to visual disability (visual acuity in best eye worse than 6/36 persisting for longer than 6 months), time to permanent motor disability (unable to walk further than 100 m unaided for six consecutive months), time to wheelchair dependency (at least 6 months duration) and time to death. Data were collected largely retrospectively through review of case records. Visual acuity in Japan is recorded using a decimal visual acuity chart for distance. A visual acuity conversion chart was therefore used to convert the Japanese decimal records into equivalent Snellen fractions.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 19. Unpaired t-tests or Mann Whitney U-tests were used when comparing two groups. The Kaplan–Meier method was used for estimating disability outcomes. Cox proportional hazards model was used to compare time-to-event characteristics. Single variable Cox regression was used to assess differences between groups. Statistical significance was set at $P < 0.05$.

Results

Demographic data

A total of 106 AQP4 seropositive patients with NMO/NMO spectrum disorder were included; 59 from the UK (Oxford and Liverpool) and 47 from Sendai, Japan. Median disease duration at last follow-up for the whole group was 75 months (range 3–417 months). Disease duration was significantly longer in the Japanese cohort than in the UK cohort (median 115 versus 60 months; mean 128 versus 92 months; $P = 0.041$). The UK cohort was mainly Caucasian (76%). The remainder were Afro-Caribbean (20%) and Asian (3%). All Japanese patients were Asian. The mean age at disease onset was 40.5±16.1 years (range 2.7–76.7 years) and this was similar in the two cohorts. The majority of patients (87%) were female: 81% of the UK cohort and 98% of the Japanese cohort. The few male patients had comparable general characteristics to the females with similar mean age at disease onset (39.4±20.9 years versus 40.6±15.5 years; $P = 0.801$) and similar disease duration (median 53 versus 75 months; mean 108 versus 104 months; $P = 0.901$). Concomitant autoimmune disorders are summarized in Supplementary Table 1.

Disease presentation and course

The majority of patients (84%) presented with either optic neuritis or LETM; only 4% presented with both (Table 1). The mean age at disease onset of patients presenting with optic neuritis was significantly younger than patients presenting with LETM (37.1±16.6 years versus 45.7±15.0 years; $P = 0.01$) and this was the case in both cohorts. Of patients with disease onset <30 years of age, 61% presented with optic neuritis compared with only 18% with LETM, whereas of patients with disease onset >50 years of age, 66% presented with LETM compared with 28% presenting with optic neuritis (Table 2).

Eighty-six per cent of the patients experienced a relapsing course (similar in both cohorts) and no patients developed a progressive stage. Overall, 49% experienced a relapse within 1 year of disease onset and 70% within 2 years. If patients started on long-term immunosuppression before their first relapse was excluded, these figures rose to 61 and 81%, respectively. Overall, the median time to first relapse was 14 months [range 1–179; 95% confidence interval (CI) 10.4–17.6]. Of note, four patients had a delay (without immunosuppressant treatment) of >10 years between disease onset and their first relapse. The mean annualized relapse rate was 0.82. Annualized relapse rate appeared to decrease with time (Supplementary Fig. 1).

Patients with a monophasic illness had a significantly shorter follow-up compared to those with relapsing disease (median 19 versus 106 months; mean 24.0±19.6 versus 121.8±90.8 months; $P < 0.001$) and were treated earlier (mean time to treatment from disease onset 2.6±5.8 months versus 54.3±6.4 months; $P = 0.003$). They were also significantly older at disease onset than those with relapsing disease (mean 50.4±15.1 versus 38.9 years±15.8 years; $P = 0.01$).

The majority of patients with a relapsing course experienced attacks of both optic neuritis and LETM (62%; i.e. developed NMO) but 18 patients (20%) had attacks of only LETM and eight (9%) experienced relapsing optic neuritis. Some patients had myelitis with short cord lesions during the course of their disease, but all such patients additionally had attacks of LETM. Forty-seven per cent of patients did not develop NMO according to the 2006 diagnostic criteria. Six patients (three from each cohort) experienced a delay of >10 years between disease onset and development of NMO.
Time to first relapse and time to NMO were not significantly influenced by gender, age at disease onset or onset attack severity. Time to first relapse was not influenced by the type of onset attack (Fig. 1A) but patients presenting with optic neuritis had a significantly greater cumulative probability of progressing to NMO over time than patients presenting with LETM (Fig. 1B).

There were no marked differences between the UK and Japanese cohorts in the proportion of onset symptoms, the percentage that developed a relapsing course, the time to first relapse, the proportion that developed NMO or the time to developing NMO. However, the mean annualized relapse rate was significantly higher in the UK cohort than in the Japanese cohort (0.97 ± 0.87 versus 0.63 ± 0.59; P = 0.020).

**Disability**

Morbidity and mortality within the whole group were substantial, with around one-fifth (18%) developing permanent visual disability, one-third (34%) developing permanent motor disability and nearly one-quarter (23%) becoming wheelchair dependent by last follow-up after median disease duration of 75 months. Nine per cent of patients died. Table 3 summarizes predictors of visual disability, motor disability and mortality.

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**Table 1** Comparison of demographic and clinical features between UK and Japanese cohorts

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>UK</th>
<th>Caucasian</th>
<th>Afro-Caribbean</th>
<th>Japanese</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>106</td>
<td>59</td>
<td>45</td>
<td>12</td>
<td>47</td>
</tr>
<tr>
<td>Mean age at onset (range)</td>
<td>40.5 (2.7–76.7)</td>
<td>40.6 (2.8–76.8)</td>
<td>44.9 (7.2–76.8)</td>
<td>28.0 (2.8–48.5)</td>
<td>40.1 (13–73)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>87%</td>
<td>81%</td>
<td>82%</td>
<td>75%</td>
<td>98%</td>
</tr>
<tr>
<td>Median disease duration (range) (months)</td>
<td>75 (3–417)</td>
<td>60 (3–417)</td>
<td>60 (3–417)</td>
<td>46 (23–174)</td>
<td>115 (7–392)</td>
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<td>Onset attack (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LETM</td>
<td>43</td>
<td>49</td>
<td>53</td>
<td>33</td>
<td>36</td>
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<tr>
<td>Optic neuritis</td>
<td>41</td>
<td>37</td>
<td>38</td>
<td>33</td>
<td>45</td>
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<tr>
<td>Optic neuritis and LETM</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Brain/brainstem</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Mixed e.g. optic neuritis and brain</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Disease course (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing</td>
<td>86</td>
<td>86</td>
<td>82</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Monophasic</td>
<td>14</td>
<td>14</td>
<td>18</td>
<td>0</td>
<td>15</td>
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<tr>
<td>Phenotype</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>NMOa</td>
<td>53</td>
<td>53</td>
<td>44</td>
<td>75</td>
<td>53</td>
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<tr>
<td>Relapsing LETM</td>
<td>17</td>
<td>20</td>
<td>25</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Relapsing optic neuritis</td>
<td>7</td>
<td>8</td>
<td>11</td>
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<td>6</td>
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<tr>
<td>Monophasic optic neuritis</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Monophasic LETM</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Monophasic brain/brainstem</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other e.g. brain and optic neuritis</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Median time to first relapse (months)</td>
<td>14</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Mean annualized relapse rate</td>
<td>0.82</td>
<td>0.97</td>
<td>0.98</td>
<td>0.97</td>
<td>0.63</td>
</tr>
<tr>
<td>Reaching visual endpoint (%)</td>
<td>18</td>
<td>22</td>
<td>16</td>
<td>42</td>
<td>12</td>
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<tr>
<td>Reaching motor disability endpoint (%)</td>
<td>34</td>
<td>46</td>
<td>49</td>
<td>33</td>
<td>18</td>
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<tr>
<td>Reaching wheelchair endpoint (%)</td>
<td>23</td>
<td>29</td>
<td>31</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Patients who died (%)</td>
<td>9</td>
<td>14</td>
<td>16</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

*a At least one attack of myelitis with LETM on spinal cord imaging and at least one attack of optic neuritis.

**Table 2** Differences in type of onset attack and disability outcomes by age at disease onset

<table>
<thead>
<tr>
<th>Onset age (years)</th>
<th>n</th>
<th>Median follow-up (range) (months)</th>
<th>Presenting with optic neuritis n (%)</th>
<th>Patients with optic neuritis-onset reaching visual endpoint n (%)</th>
<th>Patients with optic neuritis-onset reaching motor endpoint n (%)</th>
<th>Presenting with LETM n (%)</th>
<th>Patients with LETM-onset reaching motor endpoint n (%)</th>
<th>Patients with LETM-onset reaching visual endpoint n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>28</td>
<td>79 (12–394)</td>
<td>17 (61)</td>
<td>8 (47)</td>
<td>1 (6)</td>
<td>5 (18)</td>
<td>1 (20)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>30–50</td>
<td>49</td>
<td>86 (6–417)</td>
<td>18 (37)</td>
<td>4 (22)</td>
<td>4 (22)</td>
<td>4 (22)</td>
<td>9 (41)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>29</td>
<td>60 (3–229)</td>
<td>8 (28)</td>
<td>1 (12.5)</td>
<td>5 (63)</td>
<td>19 (66)</td>
<td>13 (68)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>
Visual disability

Ethnicity (see below), gender, age at disease onset and type and severity of onset attack appeared to be important predictors of permanent visual disability.

Males were significantly more likely to reach the visual disability endpoint over time than females (Fig. 2A). As there was only one male in the Japanese cohort, we also performed the analysis on the UK cohort only and the result remained the same (data not shown). Patients with optic neuritis onset were significantly more likely than those with LETM onset to develop visual disability (Fig. 2B) and patients with severe onset attacks were significantly more likely to develop visual disability over time than those presenting with non-severe attacks (Fig. 2C); this result remained significant even when stratifying for age.

Older onset patients were less likely to become visually disabled (Fig. 2D) with a hazard ratio (HR) of 0.62 for each decade of increasing age at disease onset and this remained significant even when stratifying for onset symptom type (HR 0.66 for each decade; 95% CI 0.46–0.93; \( P = 0.017 \)). Patients who reached the visual disability endpoint were significantly younger at disease onset than those who did not (mean 30.2 ± 15.7 years...
versus 42.8 ± 15.3 years, P = 0.004). Nearly half of those with disease onset < 30 years reached the visual disability endpoint (11 of 28 patients) compared with just 2 of 29 old-onset patients (onset > 50 years; Table 2). This age effect was attributable to the UK cohort (HR 0.60 for each decade; 95% CI 0.41–0.89; P = 0.003) and the Japanese cohort, visual disability was not related to onset age.

Motor outcomes

Important predictors of permanent motor disability were ethnicity (see below) and age at disease onset. Motor disability was not related to gender or onset relapse severity.

Older onset age was predictive of reaching ‘inability to walk > 100 m unaided’ outcome (Fig. 3A; HR 1.82 for each decade of increasing age at disease onset; 95% CI 1.45–2.28; P < 0.001) and becoming wheelchair dependent (Fig. 3B; HR 1.92 for each decade; 95% CI 1.34–2.74; P < 0.001). This effect was more profound in the Japanese group than in the UK group. Even when stratifying for onset relapse type, older age at disease onset was predictive of motor disability (HR 1.12 for each decade; 95% CI 1.07–1.18; P < 0.001).

Patients with a LETM-onset attack had a significantly higher probability of developing motor disability over time than patients presenting with optic neuritis (50% versus 23%; HR 3.00; 95%
CI 1.42–6.37; P = 0.004). As older patients were more likely to present with LETM, we stratified for age at disease onset, which led to this result becoming non-significant. Even patients with optic neuritis onset had a high risk of developing motor disability if age of onset was >50 years while patients with a LETM-onset presenting <30 years had a low risk of developing motor disability (Table 2). Onset attack type did not predict wheelchair dependency.

**Mortality**

Ten of the 106 patients (9.4%) died after a median disease duration (within this group) of 99 months (range 5–229) and a mean number of relapses of 4.5 (range 1–10). Death was due to NMO or complications related to NMO in 7 of the 10 patients. One patient died from choking on a food bolus as a result of impaired...
bulbar function, three severely disabled patients died from bronchopneumonia and one from sepsis, one patient died from respiratory failure after requiring home non-invasive ventilation and one patient developed respiratory failure during a severe myelitis. Of the non-NMO-related deaths, one patient died from a myocardial infarction, one from a pulmonary embolism and one from accidental choking without any history of bulbar dysfunction. The mean age at death was 52 ± 16 years (range 17–72) and older age at disease onset was strongly predictive of death (HR 2.12 per decade; 95% CI 1.29–3.49; \( P = 0.003 \)). Mortality was not associated with gender, onset attack severity or type of onset attack.

**Treatment effects**

Treatment data were incomplete for four patients, and one (Japanese) patient did not receive long term immunosuppression (defined as use of maintenance corticosteroids beyond those used to treat an acute relapse or treatment with a steroid-sparing agent). Considering the remaining 101 patients, time to treatment with immunosuppression was significantly shorter in the UK than in the Japanese cohort (mean 32.4 ± 52.2 months versus 65.3 ± 69.8 months; \( P = 0.009 \)). Twenty-three patients (15 from the UK, eight Japanese) received immunosuppression before their first relapse. These patients had a significantly longer time to first relapse than those who were not treated prior to their first relapse (median 57 months (95% CI 45.7–68.3) versus 9.0 months (95% CI 5.7–12.3); mean 74.1 versus 20.4 months; \( P < 0.001 \)). Additionally, patients who were treated before their first relapse were significantly less likely to develop NMO over time than those who were not treated before their first relapse (HR 0.371; 95% CI 0.148–0.931; \( P = 0.035 \)).

Of these 23 patients treated early, seven were left motor disabled after their index event, of which four were left wheelchair-dependent. Thus, the bias towards early treatment for those with severe onset attacks means that early therapy (treatment before the first relapse) appears to be associated with greater motor disability when compared with later treatment (Fig. 4A). This observation did not carry over to becoming wheelchair-dependent or to death. There was a trend towards early treatment being protective against development of visual disability, and in fact, no patients who were treated before their first relapse reached the visual disability endpoint (Fig. 4B).

We calculated annualized relapse rate before and after treatment with immunosuppression. Mean annualized relapse rate pretreatment (excluding the index event) was 1.34 (± 1.22). Mean annualized relapse rate post-treatment was 0.22 (± 0.43), which was a significant reduction (\( P < 0.01 \)). Fifty out of the 101 patients for whom treatment data were available had no relapses after commencing treatment (50%), over a mean follow-up period on treatment of 39.3 months.

Of note, 11 patients (two UK and nine Japanese) were treated with interferon-β prior to commencing immunosuppressant therapy. Treatment with interferon-β was generally short-lived (< 6 months in all but three patients). Interferon-β was stopped because of adverse effects in five patients and because of ongoing or increasing relapses in six patients.

The immunomodulatory and immunosuppressant treatments used in all patients are summarized in Supplementary Table 2.

**Figure 4** Kaplan–Meier curves to demonstrate effects of early prophylactic immunosuppression on disability endpoints showing (A) patients treated before their first relapse were significantly more likely to develop motor disability over time than those whose treatment was delayed (HR 4.40; 95% CI 1.83–10.61; \( P = 0.001 \)), probably because many patients presenting with myelitis reached the motor disability endpoint during the index event and were started early on immunosuppression. (B) None of the patients treated with prophylactic immunosuppression before their first relapse reached the visual endpoint, suggesting that early treatment is associated with a reduced likelihood of visual disability.
Outcomes of the United Kingdom and Japanese cohorts

Table 1 summarizes the main characteristics of each cohort. Despite the shorter follow-up time, patients from the UK cohort appeared to have more severe disease and were more likely to reach each disability endpoint than patients from the Japanese cohort (Fig. 5 and Table 1). The residual disability left by the onset attack was worse in the UK cohort. Onset LETM events were severe (unable to walk unaided at nadir) in 11 UK patients (19%) and one Japanese patient (2%). Seven patients, all from the UK, were left with permanent motor disability (unable to walk >100 m unaided) after the index event, of whom four were left wheelchair-dependent. Although more Japanese patients (n = 14; 30%) than UK patients (n = 13; 22%) had severe onset optic neuritis events (visual acuity in affected eye 6/60 or worse at nadir), the four patients left with permanent bilateral visual disability after this onset attack (visual acuity <6/36 in best eye) were all from the UK (two Caucasian, two Afro-Caribbean). Therefore, overall, none of the Japanese cohort reached any of the disability endpoints as a result of their onset attack, while 11 (19%) of the UK patients did.

There was a trend towards more patients in the UK cohort reaching the permanent visual disability endpoint over time (Fig. 5A) and overall this took a mean of 2.9 optic neuritis relapses (2.6 UK; 3.5 Japanese). The Japanese cohort had a significantly lower probability of developing motor disability and wheelchair dependence over time than the UK cohort (Fig. 5B and C). The Japanese cohort required a mean of 2.9 LETM relapses compared...
Comparisons between ethnic groups

Due to the differences noted between the UK and Japanese (all Asian) cohorts, we further divided the UK cohort into ethnic groups. Since the 59 UK patients were composed of 45 Caucasians, 12 Afro-Caribbeans and only two Asians, we looked at differences between the Caucasian, Afro-Caribbean and Japanese Asian groups, and did not include the two UK Asians.

Table 1 summarizes the differences between groups. Although the Japanese cohort was followed up for longer, there was no significant difference in the follow-up times between Caucasians and Afro-Caribbeans. There were similar gender ratios in the three groups but Afro-Caribbean patients had a significantly younger age at disease onset than Caucasians (mean 28.0 ± 13.1 years versus 44.9 ± 17.2 years; \( P = 0.003 \)) and Japanese patients (mean 40.1 ± 13.55; \( P = 0.008 \)). While mean age at disease onset did not differ significantly between Caucasians and Japanese Asians, distribution of onset age did (Fig. 6).

Afro-Caribbeans commonly had a multifocal index event involving the brain and/or brainstem (commonly including optic neuritis), but this was rare in Caucasians and the Japanese cohort (Table 1). All Afro-Caribbean patients followed a relapsing disease course compared with 2.9 in the UK cohort to become wheelchair-dependent.

The UK cohort had a greater mortality risk with time than the Japanese cohort (Fig. 5D).

Discussion

The majority of previous clinical NMO studies have included AQP4 antibody-seronegative patients, or were published prior to the availability of AQP4 assays. A few studies have sub-analysed small groups of AQP4 antibody-positive patients with NMO within their cohorts but did not include patients with atypical or limited NMO phenotypes (Bizzoco et al., 2009; Adoni et al., 2010; Akman-Demir et al., 2011; Table 4). Only one previous study has described outcomes in an AQP4 antibody-positive cohort of patients with NMO and NMO spectrum disorder (Nagaishi et al., 2011). Annualized relapse rates, final Expanded Disability Status Scale, and the proportion of patients developing visual impairment by last follow-up were noted in this Japanese cohort, but prognostic features were not investigated. Several studies have looked at prognostic markers in cohorts that included a large proportion of AQP4 antibody-seronegative patients or were unable to determine AQP4 antibody status. These are summarized in Supplementary Table 3. We are the first to report the effect of ethnicity, treatment and other baseline prognostic factors on time to visual and motor disability outcomes in two AQP4 antibody-positive populations.

Our two cohorts, in line with previously published data, showed a marked female predominance. The mean age at disease onset was similar to previous studies with the exception of some that included a high proportion of AQP4 antibody-seronegative patients and found a younger mean age at disease onset (Collongues et al., 2010; Akman-Demir et al., 2011). This may be because AQP4 antibody-seronegative patients tend to be younger than those with AQP4-mediated disease (Nagaishi et al., 2011). We found that Afro-Caribbean patients had a significantly younger age at disease onset than Caucasian or Asian patients and this may explain the younger age at onset reported in previous studies of predominantly Afro-Caribbean patients (Cabre et al., 2001; Merle et al., 2007) although in addition these reports also included seronegative patients.

Patients with optic neuritis as their onset attack were significantly younger than LETM-onset patients. All but one of the paediatric-onset patients presented with optic neuritis, while two-thirds of old-onset patients (>50 years) presented with LETM. This observation may suggest age-dependent anatomical susceptibility differences or differences in AQP4 antibody accessibility of the target organs. Optic neuritis as a younger patient phenomenon is also notable in multiple sclerosis (Scalfari et al., 2011), so the optic nerves may be generally more vulnerable to inflammatory insults in younger age groups.

A ‘classic’ Devic’s syndrome (as originally described by Devic (1894)) with simultaneous optic neuritis and transverse myelitis as the onset attack was rare in both cohorts (5 and 2% in the UK and Japanese cohorts, respectively). In contrast, higher rates have been noted when AQP4 antibody-seronegative patients are
Figure 7 Kaplan–Meier analyses of differences in outcomes between the three ethnic groups. (A) Time to first relapse was not significantly different between ethnicities. (B) Afro-Caribbeans had a greater probability of developing NMO over time than Asians (HR 2.69; 95% CI 1.21–5.96; P = 0.011). The difference between Afro-Caribbeans and Caucasians did not reach statistical significance (HR 1.47; 95% CI 0.98–2.2; P = 0.064). (C) Patients of Afro-Caribbean ethnicity had a significantly higher chance of developing visual disability (best eye worse than 6/36) than Caucasians (42% versus 16%; HR 1.83; 95% CI 1.01–3.31; P = 0.046) or Asians (12%; HR 3.69; 95% CI 1.139–12.048; P = 0.030). (D) When compared with Asians, Caucasian patients were significantly more likely to become motor disabled (inability to walk > 100 m unaided; 49% versus 18%; HR 3.85; 95% CI 1.8–8.4; P = 0.001). Afro-Caribbeans had an intermediate chance of motor disability, which was not significantly different from Caucasians or Asians. (E) Caucasians were significantly more likely to become wheelchair dependent than Asians (31% versus 15%; HR 2.819; 95% CI 1.132–7.018; P = 0.026). Afro-Caribbeans had an intermediate likelihood of becoming wheelchair dependent. (F) Asians were significantly less likely to die than Caucasians (4% versus 16%; HR 0.177; 95% CI 0.036 to 0.860; P = 0.032).
Table 4  Studies detailing demographic and clinical features of AQP4 positive patients with NMO/NMO spectrum disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>No. patients</th>
<th>Follow-up (yrs)</th>
<th>Ethnicity</th>
<th>Mean age disease onset (years)</th>
<th>Onset attack</th>
<th>Disease course</th>
<th>Time to first relapse (months)</th>
<th>Time to NMO (months)</th>
<th>Developing NMO (%)</th>
<th>Mean annualized relapse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>106</td>
<td>6.25</td>
<td>46% Asian 42% Caucasian 8% Afro-Caribbean</td>
<td>41</td>
<td>42% optic neuritis 42% LEM 5% brain/brainstem 4% optic neuritis and transverse myelitis</td>
<td>86% relapsing-remitting 14% monophasic</td>
<td>14</td>
<td>54 (17 considering only those who developed NMO)</td>
<td>53</td>
<td>0.82</td>
</tr>
<tr>
<td>Akman-Demir et al., 2011</td>
<td>21</td>
<td>8.4</td>
<td>All Turkish; not detailed</td>
<td>33</td>
<td>67% optic neuritis 24% LEM 10% optic neuritis and transverse myelitis</td>
<td>95% relapsing-remitting 5% monophasic</td>
<td>N/A</td>
<td>24</td>
<td>All by definition</td>
<td>N/A</td>
</tr>
<tr>
<td>Adoni et al., 2010</td>
<td>18</td>
<td>7.4</td>
<td>67% Afro-Caribbean 28% Caucasian 5% Asian</td>
<td>24</td>
<td>72% optic neuritis 28% transverse myelitis</td>
<td>All relapsing-remitting by definition</td>
<td>15</td>
<td>N/A</td>
<td>All by definition</td>
<td>N/A</td>
</tr>
<tr>
<td>Bizzoco et al., 2009</td>
<td>10</td>
<td>10.6</td>
<td>All Italian; not detailed</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nagaishi et al., 2011</td>
<td>583</td>
<td>4.5</td>
<td>All Japanese; not detailed</td>
<td>37</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.4</td>
</tr>
</tbody>
</table>

N/A = not applicable.
included in cohorts (Rivera et al., 2008; Bichuetti et al., 2009; Collongues et al., 2010; Akman-Demir et al., 2011). We have recently found myelin-oligodendrocyte glycoprotein antibodies in the sera of some patients with ‘classic’ Devic’s syndrome (Kitley et al., submitted for publication) and it is possible that this and other, as yet unidentified antibodies, are responsible for some cases of seronegative NMO presenting in this manner. Our current study suggests that ‘classic’ Devic’s syndrome is a relatively rare presentation of AQP4-mediated NMO and alternate diagnoses such as acute disseminated encephalomyelitis should be considered when patients present in this manner and have detectable AQP4 antibodies.

The group, of whom the majority were not started on immunosuppression after their onset attack, had a median time to first relapse of 14 months, which is similar to a small subgroup of AQP4 antibody-positive patients with NMO reported recently (Adoni et al., 2010). Overall, 49% of our patients experienced a second attack within 1 year of the onset event, 70% within 2 years. This high risk of relapse is in keeping with other studies of AQP4 antibody-positive patients with LETM and optic neuritis (Weinshenker et al., 2006; Matello et al., 2008; Collongues et al., 2011b) and supports the view that AQP4 antibody-positive patients should be offered early immunosuppressive therapy in a bid to prevent subsequent relapses. Early immunosuppressant treatment in our cohorts appeared to delay time to first relapse and annualized relapse rates were significantly lower after starting treatment. Twelve of 23 patients treated before their first relapse never had another relapse, though it should be noted that follow-up time was relatively short in such monophasic patients and it is possible that some of these would have developed relapsing disease with time. Interestingly, we encountered four patients, all with optic neuritis as their onset attack, with an interval (OFF treatment) between their onset attack and first relapse of >10 years. Two of these patients subsequently developed permanent bilateral visual disability. Fifteen patients (14%) had only a single attack of CNS inflammation over the study follow-up period and were said to have monophasic disease. This is likely a reflection of the relatively short follow-up time in this group together with the fact that long-term immunosuppression was commenced early [within 4 months of the onset attack in all patients for whom treatment data were available (n = 12) with the exception of one patient]. We found the mean annualized relapse rate to be 0.82. The decrease in annualized relapse rate over time seen in our study, and particularly after the first 2 years, may be explained by regression to the mean, treatment effects or burning out of disease activity with time. In support of treatment effects being a contributing factor, 50% of patients in our group had no relapses after commencing treatment. Due to widespread acceptance that immunosuppressive agents are effective in preventing NMO relapses, it is unlikely that any true natural history studies will be performed in NMO in the future. At present, it is not known whether it is safe to withdraw treatment after several years of disease inactivity in some patients.

Median time to developing NMO (at least one attack of both optic neuritis and transverse myelitis) was relatively long in our cohort (54 months) and six patients experienced a delay of >10 years. Patients and clinicians must therefore remain vigilant to the possibility of involvement of other parts of the nervous system even years after disease onset.

We found that patients presenting with optic neuritis had a higher probability of developing NMO with time than those presenting with LETM. However, it may be that AQP4-mediated monophasic or relapsing optic neuritis is under-recognized as many may not present to neurology services and be screened for AQP4 antibodies, whereas those with LETM are more likely to be tested. For the same reason, prophylactic immunosuppressant therapy after a first LETM attack is likely to be more common than after a single optic neuritis attack. Therefore, diagnostic and treatment differences between these two groups of patients may influence and confound disease course.

In our cohort, 47% of patients did not develop NMO according to the 2006 diagnostic criteria (Wingerchuk et al., 2006). A significant proportion experienced relapsing LETM or relapsing optic neuritis only and a small group had brain/brainstem disease. Although it is likely that some patients would have developed NMO over a longer follow-up period, these findings demonstrate that AQP4-mediated disease is not synonymous with the classical description of NMO. Thus, there needs to be further debate as to whether these phenotypes should be incorporated into NMO diagnostic criteria, or whether we should be moving towards defining NMO/NMO spectrum disorder more by AQP4 antibody status. AQP4 channelopathy disease may classify single disease pathology and be more useful, although highly specific and sensitive assays comparable across sites would be a prerequisite.

Morbidity and mortality in our cohorts were substantial, and after median disease duration of 75 months, around one-fifth had developed permanent bilateral visual disability (visual acuity worse than 6/36 in best eye), one-third permanent motor disability (unable to walk >100 m unaided) and of these nearly a quarter had become wheelchair dependent by last follow-up. Nine per cent died. Within our study, ethnicity and age at disease onset appeared to be important predictors of visual and motor disability and mortality. Additionally, male gender seemed to be predictive of worse visual outcomes.

Young-onset patients had a higher probability of developing visual disability while older-onset patients had a greater likelihood of developing motor disability. Fifty per cent of paediatric-onset patients (four of eight patients) reached the visual disability endpoint, while none developed permanent motor disability (despite 75% experiencing attacks of LETM). In contrast, only 2 of 29 old-onset patients developed visual disability, while 18 reached the motor disability endpoint. As discussed previously, onset age influenced type of onset symptom and so young patients had a ‘head start’ over older-onset patients for developing visual disability as they were more likely to present with optic neuritis, and vice versa for motor disability. However, this can only partly explain the differences in disability outcomes, as older-onset patients had an equally high risk of developing motor disability whether they presented with optic neuritis or with LETM (Table 2). Table 2 summarizes the disability risk depending on onset age and onset symptom categories. Our results suggest that there may be a lower capacity for spinal cord recovery with increasing age which could explain the worse motor outcomes in older patients presenting with LETM. However, it is less clear why older patients
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presenting with optic neuritis (where the AQP4 antibodies have already penetrated the optic nerve blood–brain barrier) had a lower risk of developing visual disability than young-onset patients. Older age at disease onset was also predictive of mortality. This may be because older age was associated with motor disability, which predisposes to life-threatening complications such as bronchopneumonia.

There was a trend towards the UK cohort having a greater likelihood of developing visual disability with time than the Japanese cohort. This appeared to be driven by poor visual outcomes in the Afro-Caribbean UK patients, who had a significantly greater likelihood of developing visual disability with time than Caucasians or the Japanese cohort. In one previous study that included AQP4 antibody-seronegative patients, visual impairment was found to be more severe and more frequent in Afro-Brazilians compared with white Brazilians (Papais-Alvarenga et al., 2002). Thus, although the number of Afro-Caribbean patients in our study was small (n = 12), thereby reducing the reliability of our results, it appears that Afro-Caribbean ethnicity may predict more severe optic nerve involvement in NMO/NMO spectrum disorder. This may be because Afro-Caribbean patients tended to present at a younger age, with onset attacks that included optic neuritis, both of which were predictors of poor visual outcomes. Additionally, subsequent attacks were also more likely to involve the optic nerves than in other ethnic groups (Supplementary Fig. 2). Due to the small numbers in this group (n = 12), it was not possible to correct for these confounders in the statistical analysis. However, we feel that it is an interesting observation whether Afro-Caribbean ethnicity results in worse visual outcomes per se, or whether Afro-Caribbean ethnicity predicts earlier age of disease onset and propensity for attacks to involve the optic nerves, which in turn predicts poor visual outcomes. Ethnicity also appeared to affect motor outcomes, with the Caucasian patients having a significantly higher probability of developing motor disability or wheelchair dependence over time than the Japanese cohort. Afro-Caribbeans had an intermediate probability of developing motor disability. Caucasians also had a higher likelihood of mortality over time than the Japanese group. It is worth mentioning that patients with NMO/NMO spectrum disorder often have severe sensory disturbance caused by cord lesions and that this may contribute to mobility problems. While we have considered inability to walk and wheelchair dependence to be motor disability outcomes, we cannot exclude the possibility that in some cases, these endpoints were reached as a result of sensory disturbance including pain (Kanamori et al., 2011). However, from a functional disability point of view, we believe that inability to walk and wheelchair dependence are important disability outcomes regardless of whether they are a result of motor weakness or sensory impairment. One interesting observation was that the proportion of patients with concomitant autoimmune disorders was much higher in the UK cohort (Supplementary Table 1) than in the Japanese cohort, and within the UK cohort particularly in Caucasians. This may be a factor in the outcome differences between the cohorts and is likely to be genetically determined. Coexisting autoimmune disease has been shown in one previous study (that may have included AQP4 antibody-seronegative patients; Wingerchuk et al., 2003) to be a predictor of disability in NMO.

Only one other study (of Japanese patients only; Nagaishi et al., 2011) has described visual and motor outcomes in seropositive patients with NMO/NMO spectrum disorder. In this study, 16.2% patients were reported as blind and 28.6% severely visually impaired after median disease duration of 4.5 years. The higher rate than the 12% seen in our Japanese group (after a longer median follow-up time in our study of 6.25 years) could be because Nagaishi et al. (2011) included those with both unilateral and bilateral visual impairment, whereas we used bilateral visual impairment as our visual endpoint. The reason for this was because we considered bilateral visual disability more functionally relevant. Mean Expanded Disability Status Scale at last follow-up in the Nagaishi et al. (2011) cohort was 5.6, but no details were provided on the proportion of patients requiring walking aids or developing wheelchair dependence and so no comparison can be made with the current study.

Although the Japanese cohort had significantly longer follow-up than the UK cohort, the UK cohort appeared to have more severe disease. In addition to the differences seen in disability outcomes between the two populations, the UK cohort also had more severe onset relapses and a higher mean annualized relapse rate. One possibility for the differences in motor and visual outcomes between the groups is the different distribution of age at disease onset (Fig. 6). Although the mean age at disease onset did not differ between Caucasian and Japanese patients, there were a greater proportion of old-onset patients within the Caucasian group. Since older age was predictive of motor disability and mortality, the differences noted in motor disability and mortality outcomes between the two groups may be explained by the fact that the Japanese cohort contained fewer ‘at risk’ older patients. Of course, this difference in age distribution may be genetically driven.

Treatment strategies used in the two populations as an explanation of the differences noted in disability outcomes need to be considered. However, although there were individual variations in immunosuppression regimes, all sites started treatment with high dose corticosteroids, tapering over several months to a similar maintenance dose. Additionally, most UK patients and some Japanese patients were also prescribed azathioprine (2.5 mg/kg). Fourteen patients (13 UK, one Japan), who were diagnosed during disease remission, commenced long-term immunosuppression with azathioprine alone, but only one patient experienced a relapse within the first 6 months of treatment. Acute relapse regimes in the two cohorts were also similar (intravenous methylprednisolone followed by an oral corticosteroid taper) although the influence of short delays in treatment cannot be assessed.

As these cohorts were not population based, we cannot rule out different referral biases between the groups, although we are unable to postulate a systematic bias to explain our findings. Additionally, the differences noted between the Caucasian and Afro-Caribbean UK patients could not be explained by different cohort referral patterns. This suggests that genetic factors are likely to influence the course and prognosis of NMO/NMO spectrum disorder. Additionally, environmental factors may also play a role.
One limitation of our study is that all patients were followed in specialist NMO clinics. This might introduce referral and follow-up biases and influence speed of diagnosis and treatment. However, the majority of patients were still from within our regional catchment areas. A further potential source of bias is differences in follow-up patterns between centres, particularly between the UK and Japan. Although all three centres follow patients closely and review patients promptly in the context of a potential relapse, we cannot completely exclude slight differences in follow-up patterns as a confounding effect. Additionally, most of the study data were collected retrospectively, which invariably introduces recall bias, particularly regarding timing and severity of relapses and speed and degree of recovery. However, because of the severe nature of the disease, we feel that it is unlikely that relapses were missed.

We chose to only include AQP4 antibody-seropositive patients. The reason for this is that it is clear from our shared experience that some patients who fulfil current clinical diagnostic criteria for NMO, but who are seronegative for AQP4 antibodies, behave very differently from AQP4 antibody-seropositive patients. We did not want to confound outcomes by including such patients. However, not including them has its disadvantages. It means that our study is not directly comparable to previous studies using clinical rather than immunological diagnostic criteria. It is also possible that we may have included some ‘false positives’ (unlike the AQP4 antibody assays used have high specificity) or excluded some ‘false negatives’ (i.e. patients with true NMO spectrum disorder).

Since all but one patient in our cohort received some form of long-term immunosuppression, this is by no means a natural history study. We feel, however, that it is still important to understand the history of treated NMO/NMO spectrum disorder as this influences management and counselling of the patients.

Finally, due to the rarity of NMO, there are statistical limitations of our study. Because of the relatively small numbers in the different subgroups, we were unable to perform corrections for multiple comparisons or undertake multivariate regression analysis. Therefore, it is difficult to fully adjust for confounding variables. Where possible, we analysed individual groups separately but small numbers meant this was not possible for all analyses. One needs to be cautious in extrapolating data from one ethnic cohort to another. However, we hope that our findings will now be used in future studies that can start with a priori hypothesis. In conclusion, we have described the disease course, visual and motor disability outcomes and mortality statistics in 106 AQP4 antibody-positive patients with NMO/NMO spectrum disorder, and compared features of a predominantly Caucasian UK cohort with that of a purely Asian Japanese cohort, and within the UK cohort have compared features between those of Caucasian and Afro-Caribbean ethnicity. We have described important characteristics of the disease course and severity and have identified predictors of time to visual and motor disability, which confirmed our preliminary observations in the first 18 AQP4 antibody-positive patients with NMO/NMO spectrum disorder seen in Oxford (Leite and Palace, oral communications). Such prognostic indicators are helpful for setting up individualized monitoring and treatment regimes. Our UK cohort appeared to have more severe disease than our Japanese cohort and within the UK cohort there were important differences between Caucasian and Afro-Caribbean patients. Thus, genetic factors are likely to be important in determining clinical outcomes in AQP4 antibody disease. This has important implications for interpreting clinical NMO studies, since clinical features and outcomes appear not to be generic across populations and may need to be tailored to individual groups. Further studies across ethnic groups are indicated. With increasing recognition of the relevance of AQP4 antibodies, earlier treatment and better outcomes are likely in the future.

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Supplementary material

Supplementary material is available at Brain online.

References


