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Neuromyelitis Optica Relapses: Race and Rate, Immunosuppression and Impairment.

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Abstract:

Objective – Neuromyelitis optica (NMO) is a rare antibody-mediated CNS disease characterised by disabling relapses leading to high morbidity and mortality. Understanding relapse activity and severity is important for treatment decisions and clinical trial design. We assessed (1) whether clinical and demographic factors associate with different relapse rates and (2) the relative impact of immunosuppressive treatments on relapse rates and on attack-related residual disability.

Methods – Clinical, demographic and treatment data were prospectively collected from 79 consecutive aquaporin 4 antibody positive patients seen in the nationally commissioned Oxford NMO service. The influence of clinical features on annualised relapse rates (using multiple regression) and the effect of immunosuppression on relapse-associated residual disability for transverse myelitis and optic neuritis attacks (using a mixed effect model) were analysed.

Results – The mean annualised relapse rate was 0.93. Relapse rates were significantly higher in Afro-Caribbeans, children and in those of shorter disease duration. Relapse rates reduced on treatment (from 0.87 to 0.42). Delay to first treatment did not influence eventual on-treatment relapse rate. Immunosuppressive treatment significantly reduced the residual disability from ON ($p<0.01$), and TM ($p=0.029$) attacks.

Conclusions – Relapse rates in NMO are influenced by multiple factors, including age, ethnicity and disease duration. Current immunosuppressive treatments reduce but do not

abolish relapses, however, they appear to additionally lessen the chronic disabling effect of a relapse.

Article:

1. INTRODUCTION.

Neuromyelitis optica spectrum disorder (NMOSD) is a rare inflammatory condition with a predilection for the optic nerve and spinal cord, and is associated with specific antibodies to aquaporin-4 water channels (AQP4Abs)[1]. Unlike multiple sclerosis, relapses are the sole cause of disability and, due to their severity, cause significant morbidity and mortality[2]. Detailed published attack data is limited. The majority of patients are treated with long-term immunosuppression in the absence of randomised controlled trial data[3]. Designing new treatment trials requires accurate attack data and a better understanding of the factors influencing attacks.

The study population is Oxford's UK-wide nationally commissioned cohort. Because AQP4Ab negative NMOSD comprise a heterogeneous group of diseases[4], analysis was restricted to AQP4Ab positive patients only.

We sought to determine a) whether clinical and demographic factors associate with different attack rates, and b) the impact of immunosuppressant treatments (IST) on relapses.

2. METHODOLOGY.

2.1 Patients

All 79 AQP4Ab positive NMOSD patients seen as part of the national NMO clinic up until April 2014 consented for their data to be prospectively collected and held on a database

(NRES ref. 10/H0606/56). Data collected included gender, age of onset, ethnicity, onset attack phenotype (transverse myelitis (TM), Optic neuritis (ON), TM and ON, attacks with brain and or brainstem involvement), visual acuities and the EDMUS grading scale (a validated simplified EDSS measure using only whole integer scores[5]).

2.2 Statistical analysis

Comparisons of mean onset age, disease duration, time to diagnosis and time to treatment for different ethnic groups was performed using a one-way ANOVA. The proportion of females by ethnic group was compared using chi-squared.

Mean annualised relapse rates (ARRs) were calculated with onset attacks included. Contribution to the ARR was determined by multiple regression analysis with independent variables for gender, age of onset (<18/adult), onset attack phenotype, ethnicity and disease duration, and interaction terms of the independent variables. The final model retained statistically significant factors for age of onset, ethnicity, disease duration and the ethnicity-by-age interaction.

Seasonal effects were assessed using the methods of Pocock 1974[6] and Roger 1977[7].

Attack severity, defined as residual disability accrued per relapse, was analysed only for TM and ON attacks because of the infrequency of other relapse types. Pre attack and pre subsequent attack disability score differences were calculated using the EDMUS score for TM and decimal visual acuity (VA, converted from UK Snellen chart) for ON. The effect of IST on attack severity was calculated. Unable to assume linearity for our outcome measures, we

repeated the analyses for only ON attacks which started with normal VA and for TM attacks starting with lower EDMUS scores (of < 6.0, because unit increases at EDSS 6 or more represent greater increases[8]). Hierarchical repeated measures models were fitted separately for changes in EDMUS and VA scores, with effects for IST ('on' or 'off') and acute treatment included to allow for this confounder (IV methylprednisolone ± plasma exchange ± intravenous immunoglobulin; 'on' or 'off'). Independent variables for ethnicity, onset age and accompanying maintenance prednisolone were also included in the model.

3. RESULTS.

The cohort was 86% female, only 54% were Caucasian, 15.2% were less than 18yrs at onset, and there was an overall median follow up of 6 years (0.44-34.4). There was no significant difference between disease duration, time to diagnosis, time to first treatment or sex, when apportioned by race. Age of onset was significantly different between ethnicities, but post-hoc analysis did not produce significant pair-wise comparisons (see supplement table e-1).

There were 372 attacks in 79 patients. The majority presented with isolated TM (38%) or ON (33%), and 10% with isolated brain or brainstem involvement. The remainder (19%) were mixed attacks. For subsequent relapses isolated TM occurred twice as frequently as ON and isolated brain/brainstem attacks occurred in only 7% of all cases (figure 1). 13 patients had monophasic disease and these had shorter follow up times and shorter times to IST.

3.1 Factors Influencing Relapse (Attack) Rates

The mean ARR was 0.93 (0.77 for patients with ≥1 year follow-up). The mean ARR includes the whole period off and on treatment for all patients. All patients eventually received IST after a variable pre-treatment period.

On inspection of ARR quartiles (table 1), Afro-Caribbeans had higher ARRs and patients presenting with brain and brainstem involvement were overrepresented in the higher ARR quartiles.

Multiple regression analysis of the ARRs indicated statistically significant effects for onset-age (paediatric/adult, $p < 0.0001$), ethnicity ($p < 0.0001$), disease duration ($p < 0.0001$) and the onset-age-by-ethnicity interaction ($p = 0.0007$). The ARR for Afro-Caribbeans was significantly higher than for Caucasians and Asians.

Paediatric-onset Afro-Caribbean's had higher ARRs than any other group, including other ethnicity paediatric-onset, and Afro-Caribbean, Caucasian and Asian adult-onset (for each, $p<0.0001$). Based on the modelling results, ARR is predicted to decline by 0.44 with every additional 10 years of disease.

ARR variability was best explained by first disease duration (23.5%), ethnicity (13.4%), the age by ethnicity interaction (11.2%) and age (9.4%). The interaction term for ethnicity and onset phenotype was not significant, suggesting independent contributions.

Only 12 patients were untreated for ≥ 4 years and their ARR declined after the onset year (see supplementary data, table e-2 & e-3).

The mean pre-all-IST ARR was 0.87 compared to the on-IST ARR of 0.42 (n=79) or 0.58 and 0.40 when only including patients with ≥1 year of data before and after treatment time (n=31).

Delay to first IST did not appear to influence eventual on-IST ARR. After a treatment delay of 2 years, ARRs reduced from 0.57 to 0.34 on treatment (n=29). Of these, in those with 1 year of follow-up (n=24), ARRs reduced from 0.75 to 0.44.

The use of individual ISTs are subject to indication bias with azathioprine plus low dose prednisolone cover being our first line choice of management. Individual treatment ARRs are given in table 2.

3.2 Seasonality

No significant seasonality effect was noted for all attacks, onset attacks, or attacks on and off treatment (supplemental data, figure e-1).

3.3 Attack Severity

Forty-eight of 136 ON attacks and 36 of 233 TM attacks had sufficient data to calculate pre- to post-attack (i.e. pre next attack) disability differences.

There was no change from pre-attack disability in 14.3% of ON attacks and 33.3% of TM attacks off maintenance IST, compared with 54.5% and 50% on IST respectively.

The modelled least squares (LS) mean change in EDMUS off IST was 2.68 (n=24, sem=0.78) and on IST was 0.05 (n=12, sem=0.94) (p=0.0291). For the subset of patients with pre-attack EDMUS <6, LS mean changes were 3.15 off IST (n=23, sem=0.64) and 1.31 on IST (n=8, sem = 1.08) (p=0.1559, see figure 2A).

For ON attacks the LS mean change in VA off IST was -0.72 (n=29, sem=0.06) and -0.30 on IST (n=17,sem=0.08) (p= 0.0008). For those with matched pre-attack VAs of 1.0 (i.e. normal VA, and the commonest starting score), changes were -0.72 off IST (n=28, sem=0.07) and -0.32 on IST (n=15, sem=0.09) respectively, confirming greater permanent worsening of vision after an off-IST attack (p=0.0007, see figure 2B).

Acute treatments (given in 78% of TM and 60% of ON attacks) did not significantly prevent attack-related disability accrual for TM or ON (p=0.46 & p=0.39, respectively) and no interaction effect was seen for acute treatment *plus* established IST (p = 0.34 (TM) & p = 0.39 (ON), respectively).

Effects of ethnicity, onset age and accompanying maintenance prednisolone did not significantly contribute to attack-related residual disability.

4. DISCUSSION.

In this study of Oxford's AQP4Ab positive cohort, childhood, Afro-Caribbean ethnicity and shorter disease duration were demonstrated to significantly associate with higher ARRs, and

immunosuppressive treatment was shown to significantly reduce the residual disability from ON and TM attacks.

The association of Afro-Caribbean race with higher relapse rates, which has not previously been demonstrated, may explain why Afro-Caribbean populations have a less favourable prognosis in NMOSD[9]. It may also explain why the mean paediatric relapse rate in another majority-Afro-Carribean cohort was 2.6, higher than our rate of 1.53[10]. Further studies are required to assess if relapse rates are lower in Asian patients and higher relapse rates in children because of low numbers in these groups. Interestingly, better outcomes and lower relapse rates have previously been noted in Japanese versus UK patients[11]. Treatment compliance should also be assessed in further studies looking at the effect of race on relapse rate.

The reported relapse rates across studies have varied and there may be many reasons for this; pre-treatment rates when noting treatment effects may include pre-selected patients with more active disease, ethnic differences across cohorts will vary, and short pre-treatment phases will artificially increase the annualised relapse rates. Our off-treatment rates are similar to those when non-treatment outcomes are reported such as pregnancy studies[12,13] and we have a long (and thus more valid) mean pre-treatment run-in period of 2.64 years.

Caution should be used in inter treatment comparisons herein in light of indication bias with non-azathioprine ISTs being more likely to be used in treatment failures. The majority of patients were on additional low dose prednisolone so we couldn't assess the effect of this addition. Twelve untreated patients had declining relapse rates over 4 years, but their untreated status may be a result of them having a milder phenotype. As previously shown,

patients may have a good outcome for many years without treatment before experiencing a disabling relapse[9].

Although IST is accepted by most to reduce relapses, of particular interest in this analysis is the observation that such treatment was also associated with reduced residual disability per relapse. This elevates the importance of immunosuppressing AQP4Ab positive patients and has consequences in designing clinical treatment trials. Acute relapse treatment (IV methylprednisolone, plasma exchange, intravenous immunoglobulin) did not appear to aid recovery from relapses, but there may be an indication bias favouring acute therapy use in high-nadir disability attacks.

Observational cohort studies have inherent limitations. Pre and on-treatment ARRs do not take into account the natural history of declining relapses, regression to the mean, and the elevation of the pre-treatment ARR in those with short pre-treatment intervals.

5. CONCLUSION.

The rate of relapse in NMOSD is influenced by multiple factors, including age of onset, ethnicity and disease duration. Immunosuppressive treatments reduce relapse rates but do not abolish attacks. Crucially, immunosuppression might have a broader role in reducing the lasting damage caused by relapses.

References

1. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006 May 22;66(10):1485–1489.

2. Wingerchuk DM, Pittock SJ, Lucchinetti CF, Lennon VA, Weinshenker BG. A secondary progressive clinical course is uncommon in neuromyelitis optica. Neurology. 2007 Feb 20;68(8):603–605.

3. Kimbrough DJ, Fujihara K, Jacob A, et al. Treatment of neuromyelitis optica: Review and recommendations. Mult Scler Relat Disord. 2012 Oct;1(4):180–187.

4. Bernard-Valnet R, Liblau RS, Vukusic S, Marignier R. Neuromyelitis optica: a positive appraisal of seronegative cases. Eur J Neurol. 2015 Dec;22(12):1511–e83.

5. Amato MP, Grimaud J, Achiti I, et al. European validation of a standardized clinical description of multiple sclerosis. J Neurol. 2004 Dec;251(12):1472–1480.

6. Pocock SJ. Harmonic Analysis Applied to Seasonal Variations in Sickness Absence. Appl Stat. 1974;23(2):103.

7. Roger JH. A Significance Test for Cyclic Trends in Incidence Data. Biometrika. 1977 Apr;64(1):152.

8. Meyer-Moock S, Feng Y-S, Maeurer M, Dippel F-W, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol. 2014 Mar 25;14(1):58.

9. Collongues N, Cabre P, Marignier R, et al. A benign form of neuromyelitis optica: does it exist? Arch Neurol. 2011 Jul;68(7):918–924.

10. Lotze TE, Northrop JL, Hutton GJ, Ross B, Schiffman JS, Hunter JV. Spectrum of Pediatric Neuromyelitis Optica. Pediatrics. 2008 Nov 1;122(5):e1039–e1047.

11. Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain. 2012 Jun 1;135(6):1834–1849.

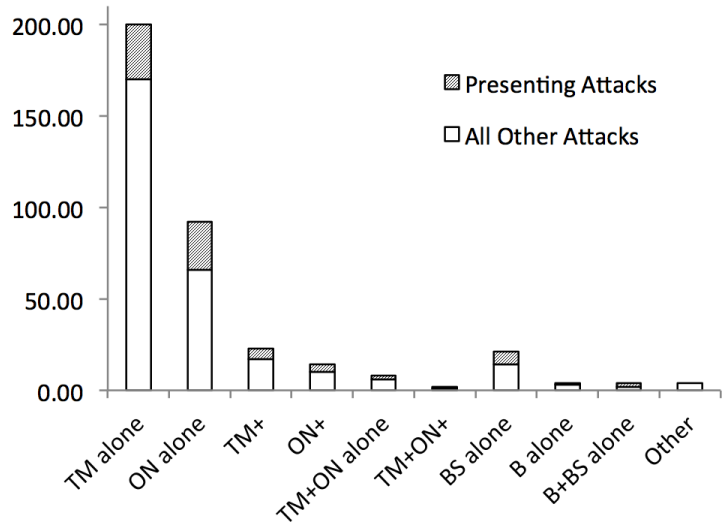
12. Bourre B, Marignier R, Zéphir H, et al. Neuromyelitis optica and pregnancy. Neurology. 2012 Mar 20;78(12):875–879.

13. Kim W, Kim S-H, Nakashima I, et al. Influence of pregnancy on neuromyelitis optica spectrum disorder. Neurology. 2012 Apr 17;78(16):1264–1267.

Figures & Tables:

Figure 1: Demographics & attack features

	n	%
Total	**79**	
Female	68	86.1
Age <18 yrs at Onset	12	15.2
Ethnicity		
Caucasian	43	54.4
Afro-Caribbean	15	19.0
Asian	9	11.4
Mixed White/Asian	1	1.3
Mixed Other	1	1.3
Not Stated/Unknown	10	12.7
Attacks (onset)	372 (79)	
TM alone (onset)	200 (30)	53.8 (38.0)
ON alone (onset)	92 (26)	24.7 (32.9)
TM *plus** (onset)	23 (6)	6.2 (7.6)
ON *plus** (onset)	14 (4)	3.8 (5.1)
TM & ON alone (onset)	8 (2)	2.2 (2.5)
TM & ON *plus** (onset)	2 (1)	0.5 (1.3)
BS alone (onset)	21 (7)	5.6 (8.9)
Brain alone (onset)	4 (1)	1.1 (1.3)
Brain & BS alone (onset)	4 (2)	1.1 (2.5)
Other (onset)	4 (0)	1.1 (0)



TM, transverse myelitis; ON, optic neuritis (unilateral or bilateral); BS, brainstem; B, brain.

* '*plus'* indicates the listed attack-phenotype did not exist in isolation but included other relapse types as part of the disease *excepting* other phenotype combinations shown in the table. For example, 'TM *plus*' refers to TM with any combination of brain, BS or other attacks but does *not* include combinations with ON which are covered in the table by 'TM & ON alone' and 'TM & ON *plus*'.

Table 1: Annualised relapse (attack) rate quartile characteristics.

	ARR <= 0.4	**ARR > 0.4 to <= 0.66**	**ARR > 0.66 to <= 1.16**	**ARR > 1.16**
Patients, n	**20**	**20**	**20**	**19**
Attacks, n (total=377)	62	94	107	109
Gender, female, n (%)	18 (26.5)	16 (23.5)	17 (25.0)	17 (25.0)
Ethnicity, n (%)				
Caucasian*	12 (27.9)	13 (30.2)	9 (20.9)	9 (20.9)
Afro-Caribbean*	1 (6.7)	3 (20.0)	5 (33.3)	6 (40.0)
Asian*	4 (44.4)	2 (22.2)	3 (33.3)	0 (0)
Other / Unknown	3 (25.0)	2 (16.7)	3 (25.0)	4 (33.3)
Onset Attack, n (%)				
TM alone	11 (36.7)	6 (20.0)	7 (23.3)	6 (20.0)
ON alone	7 (26.9)	7 (26.9)	6 (23.1)	6 (23.1)
TM & ON alone	0	0	2 (100)	0
Brain / BS *plus*	2 (9.5)	7 (33.3)	5 (23.8)	7 (33.3)
Adult / Paediatric Onset, n (%)				
Age < 18 years**	2 (18.2)	2 (18.2)	2 (18.2)	5 (45.5)
Age ≥ 18 years**	18 (26.4)	18 (26.4)	18 (26.4)	14 (20.6)

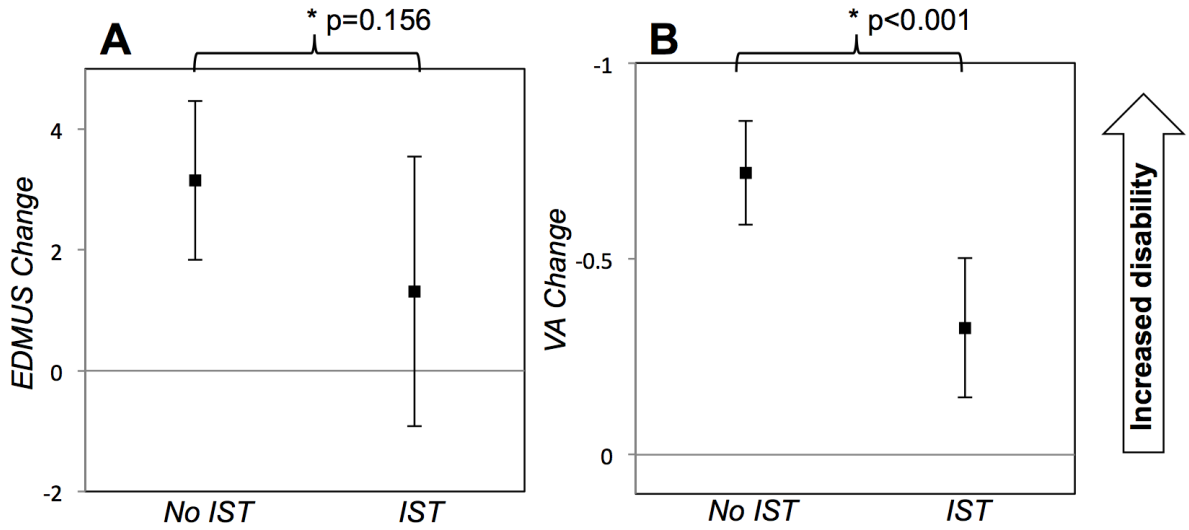
ARR, annualised relapse rate; TM, transverse myelitis; ON, optic neuritis; BS, brainstem.
* Afro-Caribbean patients had significantly higher relapse rates than Caucasian and Asians ($p < 0.01$).
** Those <18 yrs at onset had significantly higher relapse rates than those over 18 yrs at onset ($p<0.01$).

Table 2: Relative relapse rates pre-all treatment to on-treatment for individual immunosuppressants ± prednisolone.

IST	Pre All IST ARR*	On IST ARR	n	Used first-line (n)	On maintenance prednisolone, n (%) **	Mean Rx duration, yrs (sd)
Azathioprine	0.93	0.21	66	60	58 (87.9)	3.2 (4.6)
Methotrexate	1.9	0.44	16	6	15 (93.8)	3.7 (4.8)
Mycophenolate	0.76	0.50	17	4	16 (94.1)	1.4 (1.1)
Rituximab	0.76	0.46	10	1	10 (100)	1.6 (1.5)

IST, immunosuppressive therapy, ARR, annualised relapse rate, pred, prednisolone, Rx, treatment
* For each treatment group, the 'pre All IST' annualised relapse rate is calculated as the average rate for that group, prior to receiving *any* immunosuppression.

Figure 2: Relapse severity differences with and without background immunosuppression.



Change in disability scores with and without established immunosuppressive treatment. **A**. EDMUS changes representing lasting disability of transverse myelitis attacks and **B**. decimal visual acuity (VA) changes for attacks of optic neuritis. Pre-attack EDMUS scores of <6 and pre-attack VA scores of 1 used for analyses (see text). Error bars = 95% confidence intervals.
IST, established immunosuppressive treatment, e.g. azathioprine, methotrexate, etc.
NB VA change axis reversed to depict unified direction of increased disability.
* p-value for comparison of least squares means.