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Relapse Patterns in NMOSD: Evidence for Earlier Occurrence of Optic Neuritis and Possible Seasonal Variation

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Neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS) show overlap in their clinical features. We performed an analysis of relapses with the aim of determining differences between the two conditions. Cases of NMOSD and age- and sex-matched MS controls were collected from across Australia and New Zealand. Demographic and clinical information, including relapse histories, were recorded using a standard questionnaire. There were 75 cases of NMOSD and 101 MS controls. There were 328 relapses in the NMOSD cases and 375 in MS controls. Spinal cord and optic neuritis attacks were the most common relapses in both NMOSD and MS. Optic neuritis ($p < 0.001$) and area postrema relapses ($P = 0.002$) were more common in NMOSD and other brainstem attacks were more common in MS ($p < 0.001$). Prior to age 30 years, attacks of optic neuritis were more common in NMOSD than transverse myelitis. After 30 this pattern was reversed. Relapses in NMOSD were more likely to be treated with acute immunotherapies and were less likely to recover completely. Analysis by month of relapse in NMOSD showed a trend toward reduced risk of relapse in February to April compared to a peak in November to January ($P = 0.065$). Optic neuritis and transverse myelitis are the most common types of relapse in NMOSD and MS. Optic neuritis tends to occur more frequently in NMOSD prior to the age of 30, with transverse myelitis being more common thereafter. Relapses in NMOSD were more severe. A seasonal bias for relapses in spring-summer may exist in NMOSD.

Keywords: neuromyelitis optica, multiple sclerosis, aquaporin, epidemiology, relapse, seasonality

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) have been recognized as having a distinct clinical and radiological phenotype which helps to differentiate these patients from those with multiple sclerosis (MS) (1). Early studies had indicated that the pathology of these two disorders was quite distinct, with NMOSD being more destructive (2). The identification of antibodies to the water channel aquaporin-4 (AQP4) in a significant proportion of patients with NMOSD (3) has greatly aided the diagnosis and treatment of this condition. The response to both acute relapse treatments and long-term preventive therapies are quite different for NMOSD and MS.

We have previously reported on the incidence and prevalence (4), AQP4 antibody assay findings (5) and clinical features (6) of a sizeable cohort of NMOSD cases meeting the 2015 International Panel for NMO Diagnosis (IPND) diagnostic criteria (1) collected from Australia and New Zealand. Here we analyze the specific details of relapse patterns, use of acute therapies and temporal patterns both in relation to the calendar year and across the lifespan of the disease. These data are compared with an age- and sex-matched cohort of MS cases collected from the same region with the aim of identifying distinct patterns of relapse that might further assist in the early identification of cases of NMOSD and provide information about potential trigger factors.

METHODS

Case Ascertainment

This was a retrospective case-control study of NMOSD cases and MS controls. Cases of suspected NMOSD and MS were referred by a network of 23 clinical centres in Australia and New Zealand specializing in the assessment of patients with inflammatory diseases of the central nervous system in both adult and pediatric populations as previously described (4, 6). Cases of NMOSD were defined according to the 2015 IPND criteria (1). Testing for AQP4 antibodies was undertaken using either a tissue-based immunofluorescence technique or positivity on a least two cell-based assays (fixed, Euroimmun® or live, Oxford) as previously described (5). Testing for MOG antibodies was conducted using a live cell-based assay as previously described (5). Age- and sex-matched MS cases were identified from each centre with the diagnosis of MS being confirmed according to the 2010 McDonald criteria (7) with the added requirements of having no clinical features suspicious for NMOSD and being negative for AQP4 antibodies. Basic demographic and clinical features were recorded for all cases and controls as per a standardized data collection questionnaire as previously described (6). All participants provided written informed consent and the study was approved by the human research ethics committee of all participating institutions.

Relapse Definitions

For relapses, data regarding the date of onset, symptoms experienced, presumed lesion location, treatment (intravenous steroids, plasma exchange, or intravenous gammaglobulin), maximal expanded disability status scale (EDSS), visual acuity, extent of recovery (full, partial or none), laterality (unilateral, bilateral or multicentric) was recorded for each relapse. Details of symptoms were provided by the participants and where available corroborated by reference to contemporaneous medical records and MR imaging findings. The precision for the date of onset

was recorded as being either the day (date confirmed by medical records or patient diary reference), month (patient recollection or indirect medical records) or year (patient recollection). Lesion locations were based on symptomatology according to the following conventions. Motor, sensory, bladder, and pain symptoms in the limbs were attributed to a lesion of the spinal cord, unless there were additional brainstem or cerebral signs, or there was evidence of an active lesion elsewhere on MR imaging that could account for the symptoms in the absence of a relevant lesion in the spinal cord. Symptoms in the limbs with either ataxia, vestibular symptoms or cranial nerve signs were deemed to be a lesion of the brainstem/cerebellum. Hemi-motor or sensory symptoms were attributed to a lesion of the cerebral hemisphere where there was involvement of the face, cortical signs or a relevant hemispheric lesion. Blurring of vision in one or both eyes was deemed to be due to a lesion of the optic nerve, chiasm or tracts, unless there were additional brainstem signs. If symptoms could not be attributed to a single lesion site or if there was evidence of multiple active lesions on MR imaging, then lesions were deemed to be multifocal and assigned to the smallest number of regions required to explain all the symptoms. Episodes of hiccoughs, nausea and vomiting with a lesion of the area postrema evident on MR imaging were counted as area postrema relapses. Encephalitic presentations were defined as focal hemispheric symptoms or a focal hemispheric lesion associated with seizures, headache or clouding of consciousness. Classical Devic presentations were defined as the simultaneous or sequential onset (within 3 months) of optic neuritis and transverse myelitis (8).

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. Comparisons between NMOSD and MS have been made using appropriate parametric or non-parametric tests. For categorical variables, Fisher's exact test was used when the number of patients in any cell was less than five. No correction for multiple testing was undertaken. These statistical tests were performed using Statistical Package for Social Science (SPSS®) v25 (IBM®; Chicago, US). Auto regressive integrated moving average time series method was used to analyze the effect of month and seasons in the time series to predict the occurrence of relapse in MS. Relapse counts were analyzed by month using a Poisson regression model with the median month of relapse used as the reference, as has been used previously in MS (9). These analyses were performed using the STATA® statistical package v14 (StataCorp®; College Station, Texas, US).

RESULTS

NMOSD Cases and MS Controls

There were 75 cases of NMOSD with full clinical data that met the 2015 IPND criteria (1), of which 68 (91%) were positive for AQP4 antibodies. There were 101 controls with MS who were all negative for AQP4 antibodies and met the 2010 McDonald criteria (7). Testing for MOG antibodies was conducted on 42/75 (56%) of NMOSD cases, including all of the seronegative cases

TABLE 1 | Comparison of clinical features of NMOSD and MS.

Clinical feature	NMOSD	MS	*p*-value
N	75	101	
Age (Years)–median (range)	47 (19–85)	46 (16–73)	ns
Gender (Female)–*n/N* (%)	68/75 (91)	86/101 (85)	ns
Age at Onset (Years)–median (range)	40 (13–85)	32 (6–59)	0.001
Disease Duration (Years)–median (range)	4.1 (0.1–43.1)	12.3 (0.5–43.3)	<0.001
Relapses–median (range)	4 (1–16)	3 (0–11)	ns
Annualized relapse rate–median (range)	0.77 (0.13–3.33)	0.33 (0.06–3.78)	<0.001
EDSS–median (range)	4 (0–9)	2 (0–9)	<0.001
Clinical Course–*n* (%)			ns
Monophasic (CIS)	10 (13)	12 (12)	
Relapsing remitting	63 (84)	73 (72)	
Secondary progressive	2 (3)	13 (13)	
Primary progressive	0 (0)	3 (3)	
Classical Devic presentation–*n* (%)	12 (16)	9 (9)	ns
With bilateral optic neuritis	4/12 (33)	2/9 (22)	ns
Sequential (≤3 months)	6/12 (50)	1/9 (11)	ns
Recurrent	2/12 (17)	3/9 (33)	
Initial MR brain imaging normal–*n/N* (%)	12/70 (17)	3/100 (3)	0.001
LESCL on MR spine imaging–*n/N* (%)	48/71 (68)	1/89 (1)	<0.001

NMOSD, neuromyelitis optica; MS, multiple sclerosis; LESCL, longitudinally extensive spinal cord lesion; CIS, clinically isolated syndrome; SD, standard deviation; EDSS, expanded disability status scale; ns, non-significant.

and 52/101 (51%) of MS controls, and all were negative (5). The demographic and clinical features of the NMOSD cases and MS controls have been previously reported (6) and show that they were well matched for age and sex, but differ in a number of predictable clinical features as summarized in **Table 1**. Age of onset in MS cases was younger and consequently disease duration was longer. Despite this the number of relapses seen in NMOSD was greater, although not significantly, and the annualized relapse rate was approximately double that of MS controls (*p* < 0.001). The distribution of numbers of relapses in the two groups is illustrated in **Figure 1**. The level of disability at last review was greater in NMOSD compared to MS (median EDSS 4.0 vs. 2.0; *p* < 0.001). Secondary progressive disease was only seen in two cases of NMOSD and primary progressive NMOSD was not seen. The proportion of cases with monophasic disease was similar for NMOSD and MS although the extent of follow up for the MS cases was greater. The proportion of NMOSD cases experiencing a classical Devic presentation showed a trend toward being higher than in MS and these presentations were more likely to involve bilateral optic neuritis or be sequential in NMOSD, but were more commonly recurrent in MS. However, none of these differences were statistically significant due to the small numbers.

Types of Relapse

The frequency of different relapse types and lesion locations is summarized in **Table 2**. The proportions of relapse locations
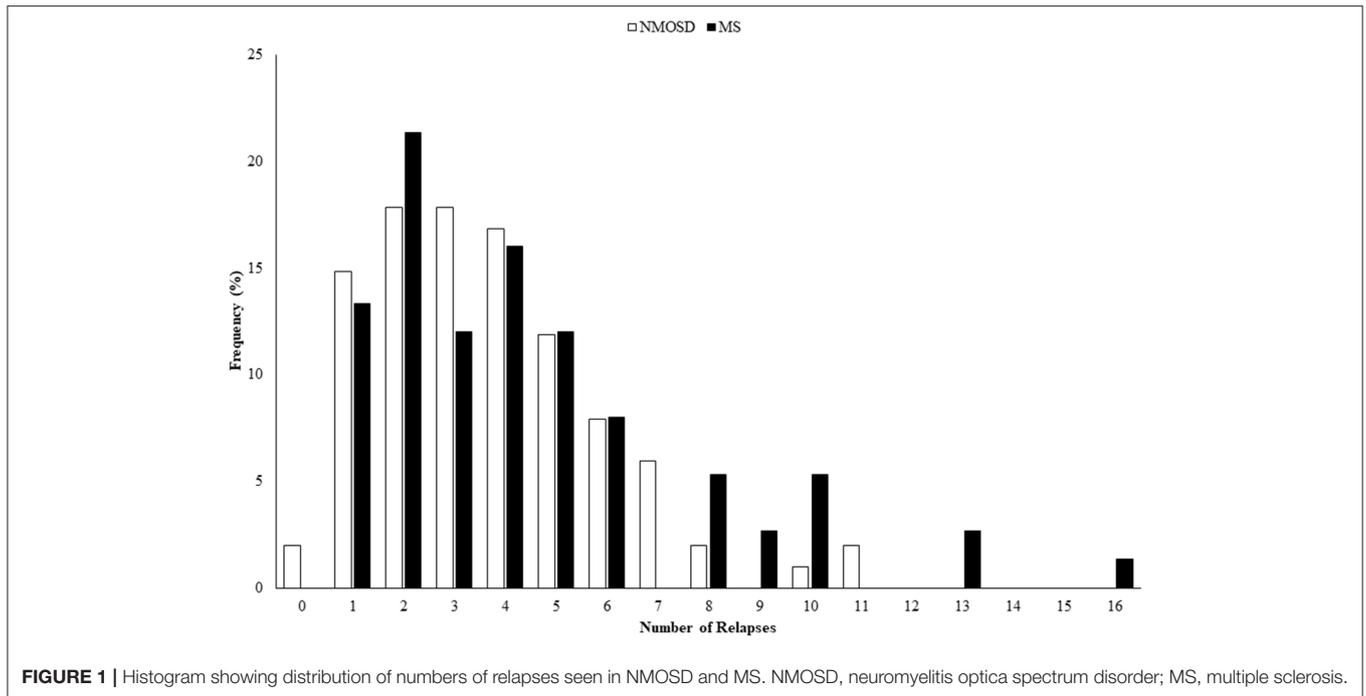
FIGURE 1 | Histogram showing distribution of numbers of relapses seen in NMOSD and MS. NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis.

TABLE 2 | Frequency of relapse locations in NMOSD and MS.

Relapse syndrome	First relapse			All relapses		
	NMOSD	**MS**	**p-value**	**NMOSD**	**MS**	**p-value**
n	75	101		329	375	
Transverse myelitis	33 (44)	51 (50)	ns	159 (48)	165 (44)	ns
Optic neuritis	29 (38)	12 (12)	<0.001	131 (40)	62 (16)	<0.001
Area postrema syndrome	7 (9)	0 (0)	0.009	11 (3)	0 (0)	0.002
Other brainstem syndrome	3 (4)	25 (25)	<0.001	16 (5)	90 (24)	<0.001
Optic neuritis and transverse myelitis	2 (2)	3 (3)	ns	7 (2)	14 (4)	ns
Cerebral syndrome	0 (0)	5 (5)	ns	2 (1)	15 (4)	ns
Optic neuritis and brainstem syndrome	0 (0)	2 (2)	ns	2 (1)	9 (2)	ns
Brainstem syndrome and transverse myelitis	1 (1)	0 (0)	ns	1 (0.3)	0 (0)	ns

NMOSD, neuromyelitis optica; MS, multiple sclerosis; ns, non-significant.

at first relapse and for all relapses were similar within the two cohorts (**Table 2**). However, there was a difference between NMOSD cases and MS controls in the frequency of optic neuritis ($p < 0.001$) and brainstem lesions ($p < 0.001$). Optic neuritis and area postrema lesions were more common in NMOSD and other brainstem lesions were more common in MS. Cerebral syndromes were rare in NMOSD and there was a trend toward these being more common in MS, but the overall numbers were lower, and this difference was not significant. There was only one encephalitis presentation seen in NMOSD. Area postrema syndromes were more common as a first relapse (9%) compared to all relapses (3%). There were no cases of NMOSD that presented with hypothermia, drowsiness or syndrome of inappropriate anti-diuretic hormone syndrome. When analyzed by sex and serostatus there were no

significant differences in the pattern of relapse in NMOSD (data not shown).

The frequency of lesion location in NMOSD according to age at the time of relapse for all relapses is shown in **Figure 2** and indicates that episodes of optic neuritis predominate at a younger age with a peak age at 20–29 years, whilst attacks of transverse myelitis predominate later with a peak incidence at 40–49 years. Relapses of all types were seen across a broad range of ages (10–69 years).

Relapse Features, Treatment and Outcomes

The principal features, treatment and outcomes for all relapses in NMOSD and MS are given in **Table 3**. The time between relapses was shorter in NMOSD (10.6 months) compared with MS (18.0

FIGURE 2 | Frequency of relapse lesion locations according to age at the time of relapse in NMOSD. NMOSD, neuromyelitis optica spectrum disorder; TM, transverse myelitis; ON, optic neuritis; BS, brainstem/cerebellar; AP, area postrema; CB, cerebral.
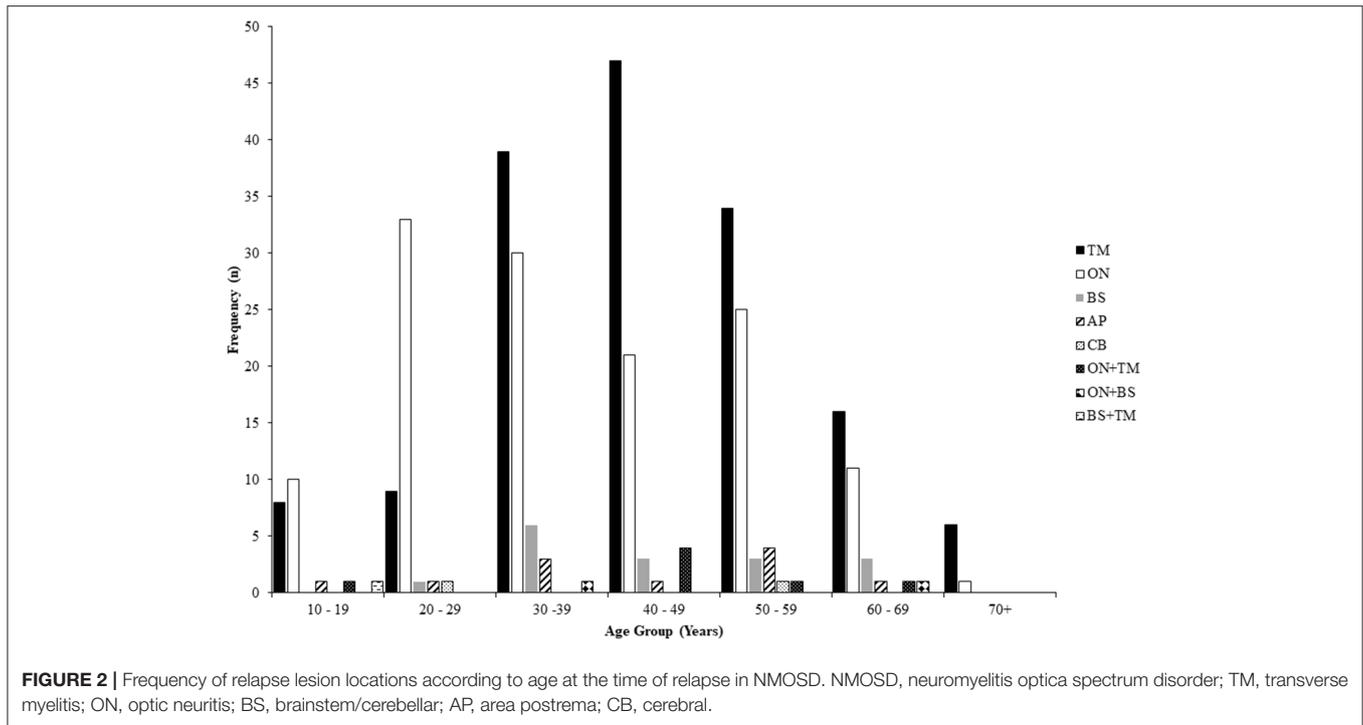
months). There was no difference in the proportion of optic neuritis attacks that were bilateral in NMOSD and MS, but the absolute frequency was higher in NMOSD (21 vs. 8). Spinal cord relapses were more commonly partial in MS. Relapse duration and maximal disability level were greater in NMOSD. NMOSD cases were more likely to be treated with high dose intravenous or oral steroids, plasma exchange and intravenous immunoglobulin. Complete recovery from a relapse was more common ($p < 0.001$) in MS (56%) than NMOSD (29%).

Seasonal Variation in Relapses

The seasonal pattern of relapses in NMOSD is shown in **Figure 3**. The auto regressive integrated moving average analysis indicated a marginal significance of month on number of relapses per month with coefficient = 0.531 C95% CI−0.678 – 1.13, $P = 0.082$) and adjusted coefficient = 3.677 (95% CI 2.034–5.320, $P < 0.001$). Poisson regression analysis indicated that no individual month significantly deviated from the median (**Figure 3**). Analysis of 3-month époques indicated a trend toward fewer relapses in February to April compared to November to January ($P = 0.065$). This corresponds to a potential peak risk of relapse in mid-spring and summer in the Southern Hemisphere and is similar to the pattern seen in MS for this part of the world (10) which has been attributed to a 1–2 month lag in relapses after the nadir of vitamin D levels (September in the Southern Hemisphere) (10).

DISCUSSION

The present data indicate that the commonest relapse types seen in NMOSD are transverse myelitis and optic neuritis and

TABLE 3 | Comparison of relapse features, treatment and outcomes in NMOSD and MS.

Relapse feature	NMOSD	MS	*p*-value
N	328	375	
Time between relapses (months)–median (range)	10.6 (0.3–336.0)	18.0 (0.5–408.4)	<0.001
Bilateral optic neuritis–*n/N* (%)	21/116 (18)	8/55 (15)	ns
Partial cord syndrome– *n/N* (%)	55/134 (41)	80/148 (54)	0.03
Relapse duration (days)–mean* (range)	68 (2–666)	50 (1–365)	<0.001
Maximal EDSS–median (range)	4 (1–10)	3 (1–8)	<0.001
Treated with IVMP–*n* (%)	193 (59)	149 (40)	<0.0001
Treated with PLEX–*n* (%)	41 (13)	0 (0)	<0.0001
Treated with IVIg–*n* (%)	20 (6)	2 (1)	<0.0001
Outcome– *n/N* (%)			<0.0001
Complete recovery	78/271 (29)	165/295 (56)	
Partial recovery	170/271 (63)	109/295 (37)	
No improvement	23/271 (8)	21/295 (7)	

Mean is given in place of median which was 30 days (1 month) for both NMOSD and MS. NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis; EDSS, expanded disability status scale; IVMP, intravenous methylprednisolone or very high dose oral steroids; PLEX, plasma exchange; IVIg, intravenous immunoglobulin; ns, non-significant.

that optic neuritis attacks, particularly as first attacks, are more common in NMOSD than MS. Area postrema presentations were exclusively seen in NMOSD and accounted for 9% of first relapses and 3% of all relapses. Attacks of optic neuritis were seen more frequently at a younger age in NMOSD with episodes of transverse myelitis occurring more frequently later. Relapse frequency, duration and severity, together with the requirement

FIGURE 3 | Rate ratio of relapses per month, using median of 29 relapses per month (September). Error bars show 95% confidence intervals (Poisson regression analysis). Y-axis plotted on logarithmic scale.
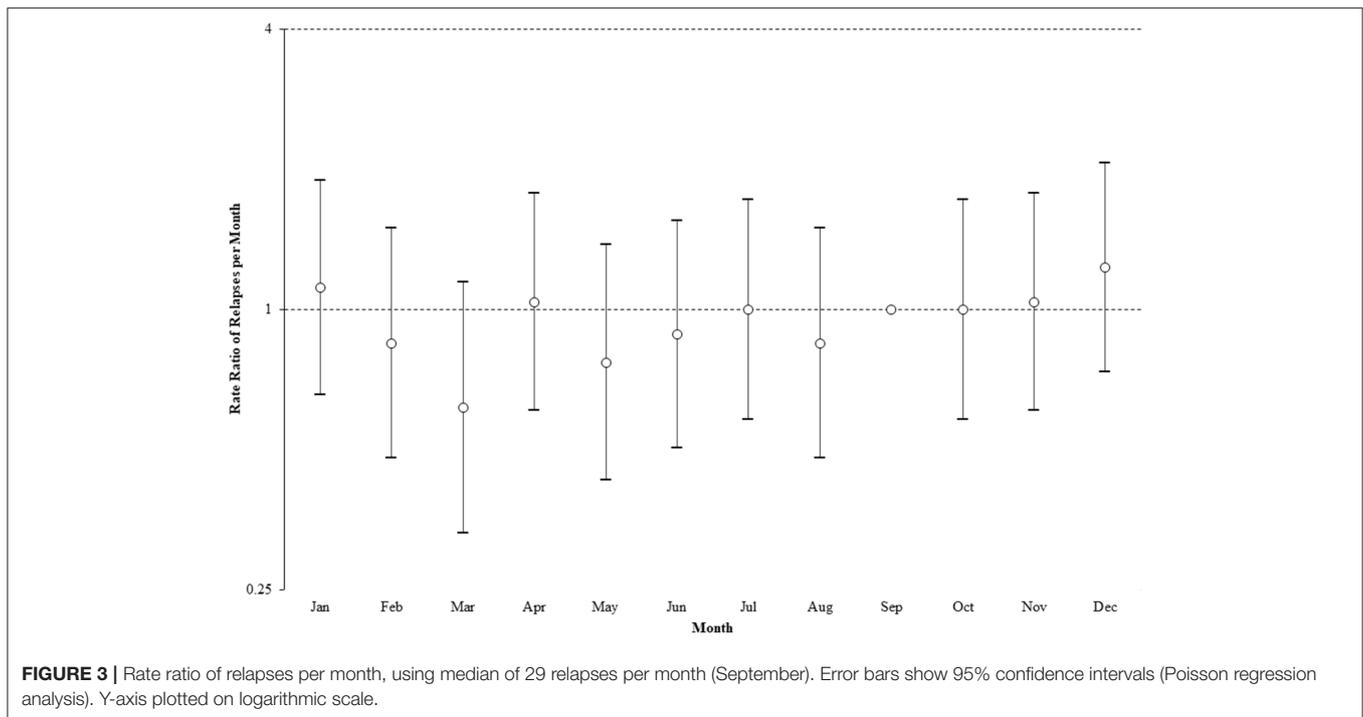
for acute immunotherapies, were all greater in NMOSD than MS. In the situation where the diagnosis of NMOSD had been established there would be a potential bias toward the use of acute immunotherapies.

As with previous studies the most frequent form of relapse in NMOSD was a lesion of the spinal cord and the frequency observed in the present study (48%) falls in the middle of previous observations (36–63%) (11–15). The frequencies of other relapse types were similar to these prior studies. As with previous studies relapses with encephalitic or other cerebral features were uncommon in NMOSD. Area postrema lesions as an initial presenting feature was seen in (9%) which was similar to prior studies (15). We found that area postrema relapses were more common at first presentation than with subsequent relapses. This finding is contrary to a recent larger study of several international cohorts (16). However, we note the definition for area postrema syndrome used in that study was broader than the definition used in the present study. No relapses involving hypothermia (17) or syndrome of inappropriate anti-diuretic hormone syndrome (18) were seen in our cohort.

Despite being an inclusion criterion for suspected NMOSD in our original clinical survey, there were eight optic neuritis attacks in our MS cohort that were bilateral. These were historical attacks and the lesion location was based on symptomatology which can be prone to error. For example, bilateral visual blurring can arise as a result of mild diplopia from a brainstem lesion or a homonymous field deficit due to a cerebral lesion. These cases otherwise had features typical for MS and were therefore not reclassified. Classical Devic presentations with either simultaneous or sequential optic neuritis and transverse myelitis were only marginally more common in NMOSD than MS and this was not a significant difference. Classical Devic

presentations were seen in 16% of NMOSD cases. The exclusion from the MS controls of cases with features suspicious for NMOSD could potentially introduce a bias in the relapse features reported here. However, we would note that the number of cases referred with NMOSD-like features that did not meet 2015 IPND criteria was similar to the number of confirmed NMOSD cases in our original survey (6), thus representing no more than 1% of all MS cases. This is unlikely to introduce any significant bias. Recall bias is always a potential issue with retrospectively collected relapse data. However, the methods used in this study were identical for the NMOSD cases and MS controls.

The frequency with which high dose steroids were administered for attacks of NMOSD (58%) was higher than in MS and was similar to previous studies (65–84%) (12, 13). The frequency of complete recovery was lower in NMOSD than MS and was in a range similar to that observed previously (13).

Two novel findings in the present study are the observation that attacks of optic neuritis predominate in younger patients with NMOSD whilst transverse myelitis is more common later in life and that there is a seasonal variation in the frequency of attacks. An earlier study has noted the predominance of optic neuritis in first presentations prior to the age of 30 years, with transverse myelitis being more common above 30 (19). We are not aware of prior data looking at seasonal variability of relapses in NMOSD. A trend toward fewer relapses from February to April compared to a peak from November to January is similar to the pattern seen in MS both in the Northern and Southern Hemisphere (9, 10). This finding is somewhat surprising considering the absence of a latitudinal gradient seen in two national studies of NMOSD prevalence (4, 20). This suggests that relative vitamin D deficiency or decreased ultraviolet

B radiation exposure are not significant factors in the risk of developing NMOSD but may be factors influencing the likelihood of relapses. These findings require confirmation in further studies.

In conclusion, we have confirmed the findings of prior studies with regard to the pattern of relapses and clinical features seen in NMOSD. We have shown that this pattern differs significantly from MS in a number of areas. There was no difference in the frequency of classical Devic presentations between NMOSD and MS, but there was a trend toward sequential and bilateral optic neuritis Devic's presentations being more common in NMOSD. The finding of optic neuritis attacks occurring more commonly at a younger age is interesting and as with the sequential optic nerve involvement with later spinal cord disease seen in classical Devic's syndrome suggests a specific vulnerability of the optic nerve early in the disease course. The increased risk of NMOSD relapse during the spring-summer suggests a seasonally dependent environmental risk factor influencing the timing of relapses in NMOSD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was reviewed and approved by Griffith University Human Research Ethics Committee (MED2009/646) and had local Governance Approval at each participating site. All participants gave written informed consent.

AUTHOR CONTRIBUTIONS

DA, MHB, SBh, SBl, MBo, KB, BB, SAB, MBr, WBr, HB, WC, CC, AC, RD, CD, DG, SHa, RH, AH, SHo, AGK, TJK, JK, CK, JL-S, CL, RM, MM, DM, PM, CO'G, JPa, JPe, JDP, KP, SWR, CS, MS, JSp, JSu, IS, BT, AV, SV, MWa, PW, EW, and RCW conceived and designed the study. EK, SAB, WBu, CB, LC, JSu, MF-P, DG, SHe, SJ, M-WL, KP, RS, JSt, BT, PW, MWo, and EY conducted the analyses. EK, WBu, and LC prepared the initial draft. AC, BB, FB, HB, RD, MF-P, SHa, SHo, JK, AJK, JL-S, PM, RM, SWR, JSi, BT, AV, SV, and PW contributed to revisions. All authors approved the final draft.

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