

Pain in patients with transverse myelitis and its relationship to aquaporin 4 antibody status

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Abstract

Pain in transverse myelitis has been poorly studied. The aim of the study was to investigate the relationship between transverse myelitis related pain and disability, quality of life, anxiety and depression, cognitive-affective states in neuromyelitis optica (NMO) patients and aquaporin4 antibody status (AQP4-Ab +ve as positive and AQP4-Ab -ve as negative). Transverse myelitis patients (44 in total; 29 AQP4-Ab +ve and 15 AQP4-Ab -ve) completed questionnaires including Pain Severity Index (PSI), Pain Catastrophising Scale (PCS), Hospital Anxiety and Depression Scale (HADS), Short Form-36 quality of life (SF-36 QOL). Clinical details such as disability, gender, age and spinal cord lesion type (short or long lesion) were noted. Correlation and multiple linear regression tests were performed using these clinical scores. Pain was found to be correlated strongly with quality of life in both groups but only correlated with disability in the AQP4-Ab +ve group. PCS, HADS and EDMUS were found to be highly correlated with pain severity using partial correlation, however, a stronger relationship between pain severity and PCS was found in the AQP4-Ab -ve group. Multiple regression analysis showed that pain severity was the most important factor for quality of life but not disability or anxiety and depression symptoms in the whole patient group. We confirm that pain is an important symptom of transverse myelitis and has more influence on quality of life than disability despite health services being predominantly focused on the latter. There may be different factors associated with pain between AQP4-Ab +ve and -ve patients.

Key Words: Neuropathic pain, quality of life, neuromyelitis optica, transverse myelitis, Aquaporin-4 antibodies

1. Introduction

Transverse Myelitis (TM) is an acute inflammatory syndrome affecting the spinal cord that can be associated with significant disability [1]. There are many different diseases that can cause TM including multiple sclerosis (MS), para-infectious syndromes and neuromyelitis optica (NMO). NMO is a disease characterised by severe relapses of optic neuritis and longitudinally extensive transverse myelitis (LETM) and is associated with a pathogenic antibody to aquaporin 4 water channels (AQP4), the discovery of which has furthered our understanding of its pathogenesis as an astrocytopathy [2-6]. Despite chronic and resistant neurogenic pain being recently recognised to be major problem in NMO [7-11], the management of transverse myelitis currently focuses on reducing disability. The occurrence of pain in NMO patients with transverse myelitis was first highlighted by Kanamori *et al.* in 2011, who noted greater pain scores and worse quality of life scores in NMO compared to MS cohorts [7]. The pain tends to be distributed in the area of sensory involvement arising from the spinal cord lesion [7, 12]. The pathogenesis of pain is unclear but involvement of spinal cord grey matter (since the lesions are centrally located), brainstem descending modulatory pathways and astrocyte damage (due to autoantibodies targeting the AQP4 water channels located on astrocyte foot processes) are all likely contributors [13]. Central mechanisms and psychological factors are also recognised factors that contribute to a chronic pain phenotype in most other pain syndromes [14, 15].

In the current exploratory study, we have investigated the relationships between clinical factors (such as mood, disability, quality of life, and

tendency to catastrophise), serum AQP4 antibodies (AQP4-Ab) and demographics (such as age) with pain intensity scores in patients who have suffered an attack of transverse myelitis seen within the national NMO service in Oxford. Because patients with AQP4-Ab have a specific pathogenesis, patients with and without this antibody were also assessed separately.

2. Methods

2.1 Patients

Myelitis patients seen within our NMO service are atypical (usually have longer lesions and more severe attacks) and include patients with the NMO antibody (AQP4-Ab) and those without. Patients with the more common typical MS TM or clinically isolated syndromes would not have been included as they are seen in MS clinics. All patients (82 in total) seen within the Oxford National NMO service in 2013 with an attack of myelitis, outside of relapse and in remission, were suitable for inclusion. The definition of a TM attack was an acute neurological attack, anatomically attributable to a lesion in the spinal cord, shown on MRI, and consistent with an inflammatory cause, including sensory symptoms \pm motor \pm bladder involvement.

Consecutive TM patients were asked to fill in questionnaires assessing pain, , anxiety and depression, quality of life and pain catastrophising scores. 50% patients returned fully completed forms in all areas and only data from these patients were analysed.

1 Data from these questionnaires was collated with their gender, age, physical
2 disability, an ambulation related score as a surrogate for spinal cord tissue
3 damage, lesion type (LETM or short lesion) and length, number of relapses
4 that was associated with the onset of pain, and their serum AQP4-Ab status.
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6 Physical disability, routinely collected from clinic visits, was assessed by the
7 European Database for Multiple Sclerosis Scores (EDMUS) [16], a whole
8 integer disability score which equates to the whole integer scores of the
9 Expanded Disability Status Scale (EDSS). Five patients with significant visual
10 impairment (at least one eye with poor vision; visual acuity on Snellen chart
11 $\leq 6/36$, and the other moderate or worse; visual acuity on Snellen chart $\leq 6/18$)
12 were highlighted because this might independently affect their quality of life
13 and mood scores. Patients were asked to score their pain outside of pain
14 associated with optic neuritis (ON).
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17 Data from 43 patients (Table 1) with myelitis: 29 AQP4-Ab +ve and 13 AQP4-
18 Ab –ve were obtained for this analysis. The antibody negative group
19 consisted of monophasic LETM (n=8, of whom 3 were myelin-
20 oligodendrocyte glycoprotein antibody positive), one NMO patient, and
21 despite being referred as NMO patients we concluded 4 probably had MS (3
22 with an optico-spinal phenotype and one with a short TM), and one further
23 patient had a monophasic short TM without any other identifiable cause.
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32 *2.2 Standard protocol approvals*

33 The use of our patient data is covered by UK IRAS ethics approval number
34 10/H0606/56, and all participants provided written informed consent.
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2.3 Questionnaires

These self-reporting questionnaires were included: Pain severity index (PSI), Hospital Anxiety and Depression Scale (HADS), Pain Catastrophising Scale (PCS), Short Form-36 (SF-36) for quality of life (QOL). These questionnaires have been used extensively in studies of pain [17-20].

2.3.1 Pain severity index (PSI). The BPI-short form (brief pain inventory) measures pain severity (four questions) and the functional impact of pain on daily functions (seven questions) including location of pain, pain medications and amount of pain relief in the past 24 hours or the past [21] [22]. Each question is scored subjectively on a scale of 0 to 10, 0 meaning no pain and 10 representing the worst pain possible[7]. Mild pain is defined as a worst pain score of 1~4, moderate pain is defined as a worst pain score of 5~6, and severe pain is defined as a worst pain score of 7~10 [21]. Combined all four pain severity scores in the questionnaire, 28 was used as severe pain threshold in the post-hoc analysis. We selected the pain severity index as a measure of pain severity for analysis.

2.3.2 Pain catastrophising scale (PCS). The current version was used in our study, developed and validated by Sullivan and colleagues [23]. The PCS measures pain intensity, emotional distress, pain-related disability, and pain behaviour. PCS was used to consider whether thoughts and feelings towards pain, are influencing the patient's perception of their pain experience. PCS is comprised of 12 questions split into three sections. It measures to what extent the patient focuses on their pain ('rumination') the extent to which the

1 patient magnifies their pain experience ('magnification') and if the patient
2 feels helpless because of their pain ('helplessness') [24]. The results of each
3 question were converted to a scale ranging from 0 being the lowest level of
4 pain catastrophising, to 4 being the highest level of pain catastrophising [24].
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6 The higher the overall score for each of the three sections, the higher the
7 level of pain catastrophising. We used the overall score of all three sections
8 as total PCS measure.
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17 2.3.3 *Hospital anxiety and depression scale (HADS)*. The HADS score [25]
18 [26] was used to examine the psychological or mental wellbeing of the NMO
19 patients. The questionnaire consists of seven questions to identify anxiety
20 and seven questions to identify depression. Grading for severity of the
21 condition, was considered as scores of 0-7, 8-10, 11-14 and 15-21, defining
22 normal, mild, moderate and severe, respectively [27, 28].
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31 2.3.4 *SF-36*. The SF-36 [29] [30] questionnaire is a set of 36 questions used
32 to measure quality of life across different disease populations. The
33 questionnaire covers physical functioning (10 questions), role limitations due
34 to physical health (4 questions), role limitations due to emotional problems (3
35 questions), energy or fatigue (5 questions), emotional well-being (5
36 questions), social functioning (2 questions), pain (2 questions)) and general
37 health (5 questions) [7]. Each question is graded from zero (worst) to 100
38 (best). We used the overall score of all 36 questions as the total measure of
39 quality of life.
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58 2.4 *Outcomes and statistical analysis*

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1 The data was tested for normality and we found that EDMUS ($p=0.001$) and
2 PCS ($p=0.001$) did not pass the Kolmogorov-Smirnov test. Therefore, in this
3 study we applied non-parametric analysis for group comparisons and
4 correlations. The Mann-Whitney test was used to explore if there were
5 significant differences between the two AQP4-Ab groups (positive and
6 negative) for EDMUS, PSI, HADS, PCS, SF36 and age.
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8 Many of the measures are inter-dependant thus in order to explore the
9 relationship between pain and individual factors (age, AQP4 status, lesion
10 type and length, number of relapses, EDMUS score, and all the
11 questionnaire scores), spearman correlations were performed without
12 correction for multiple comparisons. Because studies have shown that visual
13 impairment is linked to worse quality of life [31] we felt blindness might be a
14 confounder. Thus patients with severe visual loss (defined as a visual acuity
15 of 6/36 in one or both eyes due to optic neuritis, ON) were noted when
16 exploring the correlation between pain and quality of life. We were interested
17 in factors that might contribute to pain severity, thus from the factors that
18 correlated with pain individually and that were likely to have a causative role
19 (PCS, HADS, EDMUS) we performed partial correlations adjusting for other
20 likely confounding factors (age, gender and lesion type).
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22 As there is a strong correlation between pain score and quality of life, we
23 planned to explore how important pain was for quality of life compared to
24 other factors. A multiple linear regression model was used to determine the
25 most significant independent predictors of quality of life using the SF36 score
26 as the dependant variable, with those factors that strongly correlated
27 individually with the SF36 i.e. pain (PSI), HADS, age, PCS and disability
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(EDMUS) as independent variables. NMO is a female predominant disorder. Gender was not included in the regression analysis because there were only 8 males included the study. The residuals of the regression model were found to be normally distributed.

The partial correlations and the multiple linear regression analysis were calculated for the whole TM group. Because the AQP4-Ab positive group have a single distinct pathogenic mechanism and the AQP4-Ab negative group are heterogeneous, analysis was also performed for two separate groups. Due to the recognition of the relatively small sample size (the rarity of the condition) power analysis for this linear regression model was performed and demonstrated that with a total sample size of 43 and 5 independent variables would achieve a reasonable effect size ($f^2=0.35$) and power ($1-\beta=0.8$). Subgroup analysis of the AQP4 positive and negative groups was performed for exploratory purposes because the study was not powered to do this.

Statistical analyses were performed using SPSS Mac version 21 (SPSS Inc). All statistical tests were 2-sided and $p<0.05$ was considered statistically significant.

3. Results

Table 1 summarises the clinical characteristics and the questionnaire scores of the patients which are grouped according to their AQP4-Ab status. Although there were no significant differences between the two groups for EDMUS, PSI, HADS, PCS, SF36 and age (Mann-Whitney, Table 1), severe

1 pain severity scores (≥ 28) were seen in more AQP4-Ab positive patients
2 (34%) than those without antibodies (13%). Seventeen patients (13 AQP4-Ab
3 positive and 4 AQP4-Ab negative) were taking anti-neuropathic medications
4 (Gabapentin, Pregabalin, Carbamazepine, Oxcarbazepine or Amitriptyline); 11
5 patients were taking over the counter analgesics (6 AQP4-Ab positive and 5
6 AQP4-Ab negative) such as Paracetamol, Ibuprofen and Codeine; 9 patients
7 (all AQP4-Ab positive) were taking anti-spasmodics including Duloxetine,
8 Baclofen, Diazepam and Clonazepam.
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10 [Table 1] here
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12 The direct correlations (shown in sup Table s1~3) were performed and many
13 of the variables were found to be correlated as expected. The correlation of
14 QOL with pain severity was high in the whole group and in the subgroups.
15 Bilateral visual impairment from optic neuritis (ON) was present in four
16 AQP4-Ab +ve patients however their presence did not appear to affect the
17 association between pain and QOL (Figure 1). Not surprisingly QOL and
18 HADS, QOL and PCS, and HADS and PCS were all directly correlated. Of
19 interest, pain severity was significantly correlated with disability in the AQP4-
20 Ab positive group but not the AQP4-Ab negative group, and HADS was
21 significantly correlated with pain severity in the AQP4-Ab negative group but
22 not the AQP4-Ab positive group. The pain severity did not correlate with
23 number of relapses nor length of spine lesions in the whole group nor in the
24 AQP4-Ab positive and negative patient groups.
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26 [Figure 1] here
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28 Additional factors that correlated with pain in the whole group were EDMUS,
29 HADS and PCS therefore these were checked further by the partial
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correlation analysis. The partial correlations between pain severity and PCS, HADS and EDMUS were still significant for whole patient group after controlling for gender, age, and lesion type (Table 2). However, correlations between PSI and PCS were significantly different for antibody positive and negative groups ($p=0.05$, Table 2) with a stronger relationship in the antibody negative group.

[Table 2] here

Factors that were significantly correlated with quality of life in the whole group (PCI, EDMUS, HADS, PCS, gender and age) were used in the multiple regression analysis. The multiple linear regression analysis using quality of life as the dependant variable (Table 3), showed that for the whole group, pain severity followed by age were significant factors. When dividing the groups into AQP4-Ab positive and negative groups, pain severity ($p=0.00035$), disability score EDMUS ($p=0.015$) and HADS ($p=0.018$) were significant predictors in AQP4-Ab +ve patients; whereas in AQP4-Ab -ve patients only age ($p=0.024$) was a significant predictor.

[Table 3] here

4. Discussion

Pain in transverse myelitis has been poorly studied. This study has highlighted that pain is an important symptom in patients with previous attacks of transverse myelitis seen in an NMO clinic. Pain was also correlated with anxiety and depression, disability and pain catastrophizing behaviour and the latter appeared more dominant in AQP4-Ab negative patients. Pain rather than disability and anxiety and depression was related to quality of life in the multiple regression analysis of the whole group.

1 A previous study has shown that 46% of Japanese NMO and NMOSD
2 patients [7] had moderate or severe pain severity scores and 22% had
3 severe pain [7]. This is lower than the 58% and 34% in our UK AQP4-Ab
4 NMOSD cohort and may be explained by the previous cohort not having an
5 absolute requirement for AQP4-Ab positivity. Additionally not all our patients
6 filled in the questionnaires and there may have been a positive selection bias
7 i.e. those with more pain taking the trouble to fill in questionnaires. However
8 our figures are similar to those of one study who reported neuropathic pain in
9 62% of UK patients (the majority being AQP4-Ab positive) [9]. Of note we
10 have previously reported less disability in Japanese versus UK AQP4-Ab
11 positive patients [32] and it is possible that genetic or cultural factors (either
12 in pain interpretation itself or in pain pathology) might explain differences
13 between these ethnic groups.
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31 As in a previous study [9], we found no significant difference in the absolute
32 pain scores, disability and quality of life between AQP4-Ab positive and
33 negative groups. However, we explored further the relationship between pain
34 severity and other factors. Our results did suggest that pain catastrophising
35 behaviour had a stronger effect in antibody negative patients. The correlation
36 of pain with anxiety and depression is not surprising, and with disability
37 suggests that the pathological damage of the transverse myelitis is an
38 important factor in pain pathways.
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52 There were other differences in the relationships we studied between AQP4-
53 Ab positive and negative groups which were interesting. Individual
54 unadjusted pain correlations identified disability as significant factor only in
55 the AQP4-Ab positive group and anxiety and depression only in the AQP4-
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1 Ab negative group. With the significant difference in the association with
2 catastrophising behaviour this might suggest pain is influenced more by
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4 spinal cord pathology in AQP4-Ab positive patients and more by mood and
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6 personality in AQP4-Ab negative patients. However the small number of
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8 AQP4-Ab negative patients may reduce the power to detect an effect and the
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10 differences observed need confirming in further studies.
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15 Severe bilateral visual impairment was found only in AQP4-Ab +ve patients
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17 although the numbers were small. The pain scores from visually impaired
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19 AQP4-Ab positive patients appeared to correlate similarly with QOL than
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21 those without visual impairment. It is noteworthy that disability (mobility led
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23 and visual) appeared to associate with QOL less than pain. This is
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25 understandable because patients can adapt to physical impairment more
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27 easily than uncontrolled pain. However health service resources tend to
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29 focus more on the disability than the pain.
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35 The limitations of our observations include that only half our patients filled in
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37 all their questionnaires and a selection bias may have led to patients with
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39 more severe pain completing the scores. However this bias would have
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41 existed in both patient groups and although it could have affected the
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43 absolute scores it is unlikely to explain the relationships between the scores
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45 and there were a wide range of pain scores in both groups. Additionally, our
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47 small sample size may limit the power to see relationships with
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49 interdependence in multiple regression analysis and our multiple
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51 comparisons were not Bonferroni corrected. This was however an
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53 exploratory study to generate future hypothesis generated projects. Finally,
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55 only a general pain score rather than a neurogenic pain scale was used, thus
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1 other causes of pain could be confounders. However patients were asked to
2 score their myelitis pain (which is usually quite different from other pains) and
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4 only two of our patients (one AQP4-Ab positive and one negative) had other
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6 causes of ongoing pain i.e. arthralgia due to osteoarthritis. Removing these
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8 patients does not alter the main results.
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12 In summary our findings suggest that pain is an important factor in the quality
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14 of life experienced by both AQP4-Ab positive and negative transverse
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16 myelitis patients and suggest an even greater association than disability. A
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18 comprehensive effort to manage pain more effectively in these patients is
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20 supported. The association of an ambulation disability score (a reasonable
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22 surrogate for spinal cord tissue damage) with pain severity in this AQP4-Ab
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24 positive group supports our hypothesis that the AQP4-Ab tissue damage in
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26 the spinal cord (rather than lesion length) may be important in the
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28 pathogenesis of the resulting pain. . In contrast pain and quality of life in
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30 AQP4-Ab negative patients may be more complex and involve other factors
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32 that are less directly related to the disease pathology such as pain perception
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34 and behaviour. Thus pain management strategies in transverse myelitis
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36 patients may differ dependant on their AQP4-Ab status and this preliminary
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38 data supports the role for further research into transverse myelitis pain.
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51 **Disclosure of conflict of interest**

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55 None.
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Figure Legend

Figure 1. Quality of life (SF36) and pain severity (PSI) are significantly correlated in both the AQP4-Ab +ve group ($p=0.000007$) and AQP4-Ab -ve group ($p=0.002$). The presence of bilateral visual impairment from optic neuritis (ON, black cross) did not appear to affect this correlation in the AQP4-Ab +ve group.

Table 1. Clinical profiles in NMO patients

	Total	AQP4ab +ve	AQP4ab -ve	Mann-Whitney (p)
N	43	29	14	
Median age years (range)		52.5(23-76)	56 (28-77)	0.547
Female : male		25F 4M	10F 4M	0.51
Ethnicity(Caucasian, Asian, Afro-Caribbean)		22C/4A/3AC	11C/1A/2AC	NA
LETM: short lesion TM		20:9	9:5	0.685
Significant bilateral visual impairment (n)		4	1	
PSI		20(0-38)	15(0-34)	0.162
PCS		15(0-48)	10(0-37)	0.528
HADS		14(0-38)	13.5(5-39)	0.834
SF-36		1412.5 (65-3400)	1407 (455-3030)	0.944
EDMUS		5 (1-8)	3.5 (1-8)	0.347
Lesion length		7(0-16)	6.1(1-31)	0.664
Relapses		3(1-11)	2.5(1-11)	0.276

Median score (range)

Table 2. Correlation tests between pain and other measures

PSI correlation r (p) (Controlled by gender, age, lesion type)	PCS	HADS	EDMUS
Total group	0.51 (0.001)	0.48 (0.003)	0.41 (0.013)
AQP4ab +ve	0.38 (0.074)	0.38 (0.074)	0.45 (0.03)
AQP4ab -ve	0.81 (0.003)	0.78 (0.005)	0.20 (0.50)
Comparison between groups (p)	0.05	0.11	0.47

Table 3. Linear regression test for all factors as predictor of SF36

Factors	Total group		AQP4 ab +ve		AQP4 ab –ve	
	p	Beta	p	Beta	p	Beta
PSI	0.0002	-0.417	0.00035	-0.435	0.308	-0.342
Age	0.001	-0.304	0.186	-0.129	0.036	-0.512
HADS	0.066	-0.236	0.018	-0.330	0.943	0.028
EDMUS	0.113	-0.150	0.015	-0.270	0.935	-0.018
PCS	0.163	-0.182	0.378	-0.114	0.197	-0.558

Beta: standardised coefficients

Table s1. Full correlation tests for all measures in all groups

[illegible]

Table s2. Full correlation tests for all measures in AQP4 ve+ group

[illegible]

Table s3. Full correlation tests for all measures in AQP4 ve- group

[illegible]

Figure

