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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.

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

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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 ± motor ± 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.

Data from these questionnaires was collated with their gender, age, physical disability, an ambulation related score as a surrogate for spinal cord tissue damage, lesion type (LETM or short lesion) and length, number of relapses that was associated with the onset of pain, and their serum AQP4-Ab status. Physical disability, routinely collected from clinic visits, was assessed by the European Database for Multiple Sclerosis Scores (EDMUS) [16], a whole integer disability score which equates to the whole integer scores of the Expanded Disability Status Scale (EDSS). Five patients with significant visual impairment (at least one eye with poor vision; visual acuity on Snellen chart ≤6/36, and the other moderate or worse; visual acuity on Snellen chart ≤6/18) were highlighted because this might independently affect their quality of life and mood scores. Patients were asked to score their pain outside of pain associated with optic neuritis (ON).

Data from 43 patients (Table 1) with myelitis: 29 AQP4-Ab + ve and 13 AQP4-Ab − ve were obtained for this analysis. The antibody negative group consisted of monophasic LETM (n = 8, of whom 3 were myelin-oligodendrocyte glycoprotein antibody positive), one NMO patient, and despite being referred as NMO patients we concluded 4 probably had MS (3 with an optico-spinal phenotype and one with a short TM), and one further patient had a monophasic short TM without any other identifiable cause.

2.2. Standard protocol approvals

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

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 h 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 patient magnifies their pain experience ('magnification') and if the patient feels helpless because of their pain ('helplessness') [24]. The results of each question were converted to a scale ranging from 0 being the lowest level of pain catastrophising, to 4 being the highest level of pain catastrophising [24]. The higher the overall score for each of the three sections, the higher the level of pain catastrophising. We used the overall score of all three sections as total PCS measure.

2.3.3. Hospital Anxiety and Depression Scale (HADS)

The HADS score [25,26] was used to examine the psychological or mental wellbeing of the NMO patients. The questionnaire consists of seven questions to identify anxiety and seven questions to identify depression. Grading for severity of the condition, was considered as scores of 0–7, 8–10, 11–14 and 15–21, defining normal, mild, moderate and severe, respectively [27,28].

2.3.4. SF-36

The SF-36 [29,30] questionnaire is a set of 36 questions used to measure quality of life across different disease populations. The questionnaire covers physical functioning (10 questions), role limitations due to physical health (4 questions), role limitations due to emotional problems (3 questions), energy or fatigue (5 questions), emotional well-being (5 questions), social functioning (2 questions), pain (2 questions) and general health (5 questions) [7]. Each question is graded from zero (worst) to 100 (best). We used the overall score of all 36 questions as the total measure of quality of life.

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)	3.3.5 (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).