Journal of Neuroimmunology 283 (2015) 70–73

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Depressive state and chronic fatigue in multiple sclerosis and neuromyelitis optica

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ARTICLE INFO

Article history:
Received 8 April 2015
Received in revised form 6 May 2015
Accepted 7 May 2015

Keywords:
Neuromyelitis optica
Depression
Fatigue
Carnitine
Levocarnitine

ABSTRACT

Depression and chronic fatigue are frequently present in multiple sclerosis (MS); however, the prevalence rates have not been investigated in neuromyelitis optica (NMO). Thirty-nine consecutive NMO and 75 MS patients were compared using self-rating questionnaires for depressive states, daily activity, and fatigue, as well as serum carnitine levels. A subgroup of patients with low carnitine levels were re-evaluated regarding depression and fatigue after levocarnitine treatment. Depression and fatigue were equally prevalent in MS and NMO and were strongly correlated with one another. Measurement of the serum carnitine levels and the administration of levocarnitine did not appear to be beneficial.

1. Introduction

Depression and chronic fatigue are present in most patients with multiple sclerosis (MS) and are often described as two of the most debilitating symptoms (Tomassini et al., 2004; Tejani et al., 2012). These symptoms are thought to be caused by the disseminated demyelination. Low serum carnitine levels have been suggested to cause these symptoms, especially in MS patients treated with disease-modifying therapies (DMT) (Fukazawa et al., 1996; Lebrun et al., 2006). Carnitine is associated with transport and catabolism of fatty acids in muscle cells. By supporting transport and oxidative catabolism of fatty acids in mitochondria, carnitine contributes to muscular endurance and tolerance to fatigue. Deficiency of carnitine either by reduced intake or impaired endogenous synthesis is thought to cause easy fatigability and chronic fatigue. Oral acetyl levocarnitine (L-carnitine), administered for disabling fatigue in MS, has been investigated in various studies.

In contrast, depression, chronic fatigue and serum carnitine levels have not been assessed in patients with neuromyelitis optica (NMO), in which astrocytes are the primary target of anti-aquaporin-4 (AQP4) antibody. The effectiveness of L-carnitine for these symptoms in NMO is also unknown.

2. Methods

Seventy-five consecutive patients with MS and 39 patients with NMO who regularly visit the outpatient clinic at Tohoku University Hospital were collected between June and September 2014 to assess self-rating questionnaires for depressive states (self-reported quick inventory of depressive symptomatology: QIDS-SR) (Rush et al., 2003), daily activity (performance status: PS), and chronic fatigue (Chalder fatigue scale: ChFS) (Chalder et al., 1993). The QIDS-SR scores ranged from 0 to 27 (0 to 5: no depression; 6 to 10: mild depression; 11 to 15: moderate depression; 16 to 20: severe depression; and 21 to 27: very severe depression), whereas the PS ranged from 0 to 4 and the ChFS ranged from 0 to 56.

The serum free-carnitine, acylcarnitine, and total-carnitine levels were measured for once at the same time of the questionnaires. The scores regarding gait disturbance (GD) and optic neuritis (ON), and the final expanded disability status scale (EDSS) were also collected. The GD-score scales were as follows: 0: normal; 1: only slight GD without impaired ADL; 2: possible to walk but with impaired daily activities; 3: wheelchair-bound; and 4: bedridden. The ON-score scales in each side of the eye were as follows: 0: normal; 1: possible to read; 2: counting finger; 3: hand motion or light perception; and 4: blindness. In NMO, the dose of oral prednisolone (PSL) was also collected.

Pearson correlation coefficients or Spearman rank correlation coefficients (R) were comprehensively compared between all pairs of datasets to identify mutual relations and confounders. Pearson's R was adopted for the variables with normal distributions, and Spearman's R was adopted for the other pairs.

Eleven patients with low carnitine levels (six MS and five NMO patients) who agreed to L-carnitine (1800 mg/day) treatment were followed, and their questionnaire scores were assessed after one month of administration.

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http://dx.doi.org/10.1016/j.jneuroim.2015.05.007
0165-5728/

All statistical analyses in this study were conducted using SPSS (Statistical Package for the Social Sciences) Statistics Base 22 software (IBM, Armonk, New York, USA) and Microsoft Excel Statistical Analysis (ver. 6.0; Esumi Co., Ltd., Tokyo, Japan).

This study was approved by the local research ethics committees of Tohoku University School of Medicine and of Tohoku University Hospital. Each patient voluntary gave written informed consent before participating in the study and also before treatment.

3. Results

3.1. Demographic and laboratory data

Of the 75 MS patients, 13 (17.3%) patients were male and 62 (82.7%) patients were female (Table 1). All 39 NMO patients were female. The mean present age was increased in NMO compared with MS ($p < 0.0001$). The median disease duration was similar in MS and NMO ($p \geq 0.10$). The median of the final EDSS was increased in NMO compared with MS ($p < 0.0001$). In the MS patients, there was a significant correlation between the disease duration and the final EDSS ($R = 0.29$, $p < 0.01$). Eight of the 75 MS patients (10.7%) and 16 of the 39 NMO patients (41.0%) were taking anti-depressant medications at the timing of this study.

3.2. Self-rated questionnaires

More severe than mild levels of depression (QIDS-SR ≥ 5) were identified in 47 MS patients (62.7%) and 29 NMO patients (74.4%). Impaired daily activity (PS ≥ 1) was identified in 42 MS patients (56.0%) and 30 NMO patients (76.9%) (Table 1). If the cut-off level of the ChFS was set at a conventional score of 26, abnormal chronic fatigue (ChFS ≥ 26) was suggested in 53 MS patients (70.7%) and 30 NMO patients (76.9%). There was no significant difference between MS and NMO in the QIDS-SR ($p \geq 0.10$) or ChFS ($p \geq 0.10$); however, the PS was increased in NMO ($p < 0.05$). Strong correlations were identified between depression (QIDS-SR) and fatigue (ChFS) in both MS and NMO (Fig. 1).

3.3. Serum carnitine levels

A low-level of total-carnitine (normal range: 45–91 μmol/L) was identified in 17 MS patients (22.7%) and 8 NMO patients (20.5%) (Table 1). A low-level of free-carnitine (normal range: 36–74 μmol/L) was identified in 13 MS patients (17.3%) and 7 NMO patients (17.9%). A low-level of acylcarnitine (normal range: 6–23 μmol/L) was identified in 13 MS patients (17.3%) and 4 NMO patients (10.3%).

Table 1
Comparisons of the clinical and laboratory information between MS and NMO.

	MS (n = 75)	NMO (n = 39)	p-Value
Present age (mean ± SD)	36.4 ± 3.1	51.9 ± 13.6	<0.0001
Duration [years] (median, range)	6 (1–31)	8 (0–35)	n.s.
ON-score (median, range)	0 (0–4)	2 (0–8)	<0.0001
GD-score (median, range)	1 (0–3)	1 (0–4)	n.s.
Final EDSS (median, range)	2 (0–8)	4.75 (0–8.5)	<0.0001
QIDS-SR (median, range)	6 (0–24)	6 (1–23)	n.s.
PS (median, range)	1 (0–3)	1 (0–4)	0.0106
ChFS (median, range)	31 (16–54)	32 (18–55)	n.s.
Total-carnitine [μmol/l] (mean ± SD)	53.8 ± 10.9	53.3 ± 9.0	n.s.
Free-carnitine [μmol/l] (mean ± SD)	44.3 ± 9.8	44.2 ± 8.2	n.s.
Acyl-carnitine [μmol/l] (mean ± SD)	9.6 ± 3.8	9.1 ± 2.4	n.s.

Abbreviations; MS: multiple sclerosis, NMO: neuromyelitis optica, SD: standard deviation, n.s.: not significant with $p \geq 0.05$, QIDS-SR: quick inventory of depressive symptomatology (self-reported), PS: performance status, ChFS: Chalder fatigue scale.

3.4. Correlations between carnitine levels and questionnaires

The correlation coefficients between the serum carnitine levels and the three self-rated questionnaires were not significant ($p \geq 0.10$) between any pairs.

3.5. Correlative coefficients with clinical information

The QIDS-SR ($R = 0.331$, $p < 0.05$) and ChFS ($R = 0.397$, $p < 0.05$) exhibited weak to moderate correlations with disease duration in NMO (Fig. 2A, B), but not in MS (Fig. 2C, D). In contrast, the QIDS-SR ($R = 0.373$, $p < 0.05$) and ChFS ($R = 0.307$, $0.05 \leq p < 0.10$) exhibited weak to moderate correlations with the GD-score in MS, but not in NMO. There was no significant correlation between ON-score and self-rating questionnaires including QIDS-SR both in MS and NMO patients. Strong correlations between the final EDSS and PS were identified in both MS and NMO. A moderate correlation between the free-carnitine level and present age was identified only in NMO ($R = 0.485$, $p < 0.01$).

The final EDSS exhibited weak correlations with disease duration in MS ($R = 0.306$, $p < 0.01$) and present age in NMO ($R = 0.399$, $p < 0.05$). In NMO patients, QIDS-SR score was significantly higher in those with anti-depressants than in those without anti-depressants ($p \leq 0.01$). However, results did not change even among patients without anti-depressants.

3.6. Carnitine levels and self-rating questionnaires by treatment types

In the MS patients, the free-carnitine level was lower in the patients receiving no treatment ($n = 7$; 36.6 ± 8.5 μmol/l) compared with the patients receiving disease-modifying treatments (DMT) ($n = 68$; 45.1 ± 9.6 μmol/l; $p < 0.05$). QIDS-SR was significantly lower in the MS patients administered IFN-β (median: 4; range: 0–17) compared with the patients administered fingolimod (7; 1–20) ($p < 0.05$), most likely because of the selection-bias for fingolimod in patients with depressive symptoms who avoid IFN-β.

In NMO, 36 patients (92.3%) were administered low dose oral PSL therapy. There was no significant correlation between the PSL dose and the carnitine levels ($p \geq 0.05$ for both free- and acyl-carnitine). No correlation was identified between the PSL dose and the questionnaires.

3.7. Changes after L-carnitine therapy

Six MS patients and five NMO patients with a low-level of serum carnitine were administered L-carnitine. There was no significant improvement in any questionnaire after the treatment as shown in Fig. 3 ($p \geq 0.10$).

4. Discussion

This study demonstrated for the first time that NMO patients experience comparable levels of depressive state and chronic fatigue as MS patients. Because few reports have described cerebral demyelinating lesions in NMO, other mechanisms are needed to explain this finding. The oral PSL dose and present age are not likely mechanisms because they did not exhibit correlations with the scores although, longer disease duration would contribute to the advent of chronic depression and fatigue in NMO.

Although the same levels of depression and fatigue were identified in MS and NMO, the mechanisms of these symptoms could be different between the diseases. For example, gait disturbances exhibited significant correlations with the QIDS-SR and close to significant correlations with the ChFS in MS, but not in NMO. In contrast, disease duration exhibited significant correlations with the QIDS-SR and ChFS in NMO, but not in MS. These findings suggest that chronic depression and fatigue in MS could be caused by the same pathomechanism of