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ORIGINAL PAPER

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Neuropsychological deficits but not coping strategies are related to physical disability in multiple sclerosis

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Abstract Detailed neuropsychological assessment was performed in 86 women (48 patients with stable relapsing-remitting multiple sclerosis (MS) and 38 matched healthy controls (HC)). Patients were categorized into patients without (EDSS ≤ 1, $n = 26$) and with physical disability (EDSS ≥ 2, $n = 22$). Patients with EDSS ≥ 2 scored significantly ($P < 0.05$) higher in Beck's depression inventory (BDI) and depression scores (DS) compared to HC and patients with EDSS ≤ 1. No significant differences were found with respect to the use of specific coping strategies between the patient groups, who preferred active (EDSS ≤ 1) or distracting (EDSS ≥ 2) strategies. Cognitive deficits were significantly increased in MS with EDSS ≥ 2 with regard to visuo-construction and visual memory, in particular with respect to geometric figures, compared to MS with EDSS ≤ 1. Significant positive correlations of depression variables (BDI, DS and BL) and depressive as well as denying coping strategies were found. Our results showed increased depression scores and increased cognitive deficits in advanced physically disabled patients, without selection of specific coping strategies. This supports an individual MS-specific neuropsychological therapeutic approach in order to improve disease related deficits together with social functioning.

Key words cognition · coping · depression · multiple sclerosis · neuropsychological tests

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Introduction

Multiple sclerosis (MS) is hallmarked by inflammatory myelin lesions and axonal loss of the central nervous system. While axonal lesions are associated with irreversible loss of functions, inflammatory demyelination is related to acute but reversible neuronal damage [7, 8, 43]. In parallel to physical disabilities, impairment of neuropsychological functions, including memory and mood were found in up to 2/3 of all MS patients [17, 22, 23, 41, 46]. Cognitive decline in MS was considered to be associated with increased physical disability and affective impairment [23, 29, 39]. With regard to memory performance, already disease duration of less than 2 years was found to result in impaired memory, including visual, verbal and short-term memory [1, 2, 21, 28], as well as attention [43, 45]. In particular short-term memory dysfunction has been described to affect visuo-spatial more than verbal capabilities [20, 45]. Although depression seemed to be less closely related to morphological changes, marked differences compared to healthy subjects were found [7–9, 40, 43]. Due to the nature of the disease individual course, grade of physical impairment, relapse rate and frequency influenced neuropsychological test results [25, 30]. In physically disabled patients (EDSS > 2, according to Kurtzke's Expanded Disability Status Scale) with long-standing progressive MS, cognitive deficits appeared more pronounced than in early stage MS. However, if tested thoroughly, depression and impaired cognition were found in up to 60% of all patients already at EDSS < 2 [16, 17, 20, 36, 41]. At this early stage diagnosis

puts a high psychological burden on these relatively young patients and effective coping with symptoms and signs of the disease is highly relevant for their functioning and quality of life. The selection of specific coping strategies was found partly dependent on gender [31, 33], personality traits [32], as well as on the type of chronic disease [33, 42]. In MS, female patients were found to show the highest depression scores together with the lowest score of satisfaction. These patients favoured active-problem-oriented coping strategies and seeked social support, in particular [31]. However, compared to other chronic diseases like myocardial infarction, end-stage renal failure and cancer, MS patients were found to differ little with respect to their preferred coping strategies [33].

The present study assessed in how far cognitive deficits and depression can be found in MS patients depending on the grade of physical disability and if specific coping strategies were chosen in relation to the burden of the disease.

Methods

Subjects

In order to certify a homogeneous study population only woman were included into this study. The group consisted of 48 female out-clinic patients (mean age: 35 years, range: 23–52 years) with relapsing-remitting, clinically definite or laboratory-supported MS, according to Poser's criteria. At time of testing, all patients had stable MS with variable physical disability (EDSS 0–6, mean 1.5 ± 1.6) with a stable socio-economic background. Patients gave their informed consent to participate in the study, which had been approved by the local ethics committee.

In order to evaluate the dynamic relation between physical, cognitive and emotional impairments, we formed two groups of patients: MS group 1, EDSS ≤ 1 (n = 26; aged 34 ± years, IQ 103 ± 7.8; including EDSS 0: n = 16; EDSS 1: n = 10; mean EDSS: 0.4 ± 0.5) and MS group 2, EDSS ≥ 2 (n = 22; aged 36 ± 6 years; IQ 108.5 ± 8.3; mean EDSS 2.8 ± 1.4) and compared them with matched healthy women as controls (HC: n = 38; aged: 33 ± 6 years; IQ 105.4 ± 9.2). No subject had a history of psychiatric or other neurological disorders at the time of testing. All subjects had been free of medication affecting the central nervous system, including corticosteroids for at least 4 weeks. Immunomodulatory therapies included azathioprin (n = 5), interferon-beta (n = 8) and glatiramer-acetate (n = 2). No patient with EDSS = 0 was on any therapy, compared to eight patients with EDSS of 1; 3 patients with EDSS 2 and four patients with EDSS ≥ 3.

For intelligence assessment all subjects completed a short version of the German Wechsler Adult Intelligence Scales. This version is based on performance in the subtests: General knowledge, similarities, picture completion and block design. The block design subtest was excluded for determining the general intellectual functioning, since it puts MS patients at a disadvantage due to motor speed demands [25]. IQ-scoring was computed as the mean of the IQs based on general knowledge, similarities and picture completion, revealing no differences between patients and healthy controls with regard to age and IQ.

Affective and coping measurements

A mood rating scale (MRS) was used to assess actual mood by using the Bond-Lader visual analogue scales. Sixteen paired pronouns were analysed and averaged, resulting in high scores if mood was negatively affected. Von Zerssen's depression scales (DS) are self-rating scales with two parallel forms to calculate the mean value of depression (DS), somatic/physical complaints (BL) illustrating somatic complaints regardless the causes and the actual mood (BFS) at time of testing [47]. This test was complemented by standard Beck's-Depression-Inventory (BDI) [6]. Freiburg's coping questionnaire (FPI) was used in patients as a validated tool to differentiate various coping strategies like depressive/detractive reactions from active/problem-solving, distractive/reconstructive behaviour, denial/wishful-thinking and superstitious/religious coping strategies based on a list of 35 items [33, 37].

Cognitive measurements

Visuo-spatial short-term memory was assessed by nonverbal Kimura's Recurring-Figures Test (RFT) using two sorts of abstract drawings: geometric and nonsense drawings. Every card was shown for up to 3 s and should be stored in memory. "Recurrent figures" were shown repeatedly. In case of remembering such a drawing, the person should react verbally. Three variables were evaluated by their correct, false and total score, namely geometric figures, nonsense figures and all figures as a sum of correct and falsely remembered recurrent figures [26]. This was complemented by recognition memory test for faces (RMF) presenting 50 pairs faces to be judged as sympathetic or not. Recognition at representation of a known face in conjunction with an unknown one, provides a total score of RMF visual memory function. To assess the visuo-spatial/visuo-constructive functioning, the mosaic test (MT) was used, as part of the standardized Wechsler Intelligence Scale (WIP). The sum of points achieved was transformed into IQ-values, afterwards the variable MT was the extracted and analysed.

Statistics

Statistical analyses were performed using SPSS version 12.02. Group differences were evaluated by analysis of variance (ANOVA, F). If there were significant group differences in variances, non-parametric tests (Kruskal–Wallis ANOVA, H) were used. Post-hoc paired group comparisons were carried out using the strict Bonferroni's alpha correction or, in case of nonparametric analysing, Mann–Whitney U-tests, respectively. Nonparametric correlation was calculated using Spearman-Rho coefficient factor. Significance was considered, if $P < 0.05$.

Results

Affective variables and coping

Mean and standard deviation (SD) of statistical different affective variables, including depression (DS), somatic/physical (BL) and mood (BFS) complaints, Beck's depression inventory (BDI) are shown in Fig. 1. Significant differences were found for patients with EDSS ≥ 2 who showed higher depressions scores with regard to Beck's depression inventory (BDI, $P = 0.015$); von Zerrssen's depression score (DS, $P < 0.01$) and the somatic complaint list (BL, $P = 0.046$) compared to healthy controls (HC). If compared to patients without physical disability (EDSS ≤ 1), disabled patients showed significant differences with regard to BDI ($P = 0.029$) and DS ($P = 0.042$), respectively. Patients without disability scored higher on BL ($P < 0.001$) compared to HC, only. No differences between patient groups and

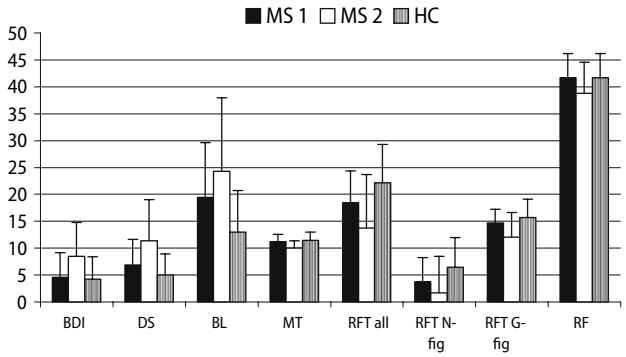

Fig. 1 Statistically different neuropsychological variables of MS patient groups and healthy controls. MS 1: EDSS ≤ 1; MS 2: EDSS ≥ 2; HC-healthy control subjects. BDI—Beck's depression inventory showed significant differences between HC and MS 2 ($P = 0.015$) and MS 1 and MS 2 ($P = 0.029$); DS—Von Zerssen's Depression score showed significant differences between HC and MS 2 ($P < 0.001$) and MS 1 and MS 2 ($P = 0.042$) as well as in the complaint list (BL) which showed significant differences between HC and MS 1 ($P = 0.046$) and MS 2 ($P < 0.001$); MT—Mosaic test showed significant differences between HC and MS 2 ($P < 0.001$) and MS 1 and MS 2 ($P = 0.018$; note a factor of 10 for all values displayed to allow simple scaling); RFT—Recurrent figure test showed significant differences between HC and MS 2 ($P < 0.001$) as well for nonsense figures (RFT N-fig, $P = 0.006$) as for geometric figures (RFT-G-fig, $P = 0.001$, including differences for MS 1 and MS 2 ($P = 0.009$); RF—Recognition of faces showed significant differences between HC and MS 2 ($P = 0.039$)

controls were found with respect to preferred coping strategies and mood rating scales.

Preferred coping strategies found for MS patients with EDSS ≤ 1 were active (3.42 ± 0.90), followed by distracting (3.11 ± 0.85), religious (2.65 ± 0.83), depressive (1.92 ± 0.5) and denying (1.72 ± 0.69); for MS patients with EDSS ≥ 2 they were distracting (3.36 ± 0.77), active (3.28 ± 0.94), religious (2.64 ± 0.87), denying (2.34 ± 1.10) and depressive (1.99 ± 0.84), respectively.

No significant differences were found with respect to any coping strategy used by either MS patients with EDSS ≥ 2 or MS patients with EDSS ≤ 1. Coping in the way of depressive and illusive strategies correlated significantly and positively with each others as well as with depression scores (BDI, DS and BL: $P < 0.001$), while active-problem solving and distracting strategies remained uncorrelated to depression scores. No correlation of coping or affective variables with cognitive deficits were found (data not displayed).

Cognitive variables

Patients with EDSS ≥ 2 showed significant differences with respect to visual memory, i.e. facial recognition ($P = 0.039$) and overall recurrent figure tests. These patients scored significantly worse with regard to recognition of all figures ($P < 0.001$), to falsely recognized geometric figures ($P = 0.001$), as well to all geometric ($P < 0.01$) and nonsense figures ($P < 0.006$), compared to HC. Compared to patients with EDSS ≤ 1 physically disabled patients scored lower with respect to falsely ($P = 0.009$) and all ($P < 0.029$) recognized geometric recurrent figures. With respect to visuo-spatial/visuo-constructive functioning, patients with EDSS ≥ 2 performed significantly worse with respect to (Mosaic test) MT compared to HC ($P = 0.001$) as well as to patients with EDSS ≤ 1 ($P = 0.018$). Significant differences in visuo-spatial memory and visuo-constructive test results were presented in Fig. 1.

Discussion

Several differences were found between both groups of MS patients (EDSS ≤ 1 and EDSS ≥ 2) and healthy control subjects (HC). With respect to cognitive functions, more advanced physically disabled MS patients (EDSS ≥ 2) showed significantly impaired visuo-constructive functions and short-term recognition memory compared to HC. In other studies, we had shown, that those deficits were already present in patients without any physical disability (EDSS 0), although it appeared to be more pronounced in patients with increasing EDSS of > 2 [20, 22, 45]. However, the present study indicated cognitive changes beyond physical impairment of an EDSS of 2, indicating an imbalance of physical disease progression measured by a disability score (EDSS), which stresses ambulation rather than neuropsychological function. With respect to sustained effects of MS-related impairment, cognition but not depression seemed to be affected, consequently [1, 22, 28]. Our findings are consistent with other studies on cognitive deficits in MS, particularly with those on memory dysfunction. In mildly disabled MS patients impaired recall was found to be a reliable and robust phenomenon [2, 29, 30] in contrary to verbal learning [10]. Those deficits have been attributed to lesions in frontal and temporal lobes of MS-patients [4, 5], supported by the evidence that the right temporal lobe supports visual memory performance whereas the left temporal lobe supports verbal memory performance, preferentially [3–5, 38]. Deficits in attention seemed to play a similar important role, in particular, in otherwise not-disabled MS-patients and exerted important influence on other memory functions [11–13, 15, 34, 45]. With respect to emotional disturbances following the diagnosis of MS and the need to adjust mentally, high emotional distress ay cause depression and anxiety in these young female patients with uncertainty with respect to the course of the disease [14]. Psychological adjustment and depressive coping may have more important impact on daily functioning than major depression [16–18, 27, 31–33, 36, 41]. In keeping with others, no single coping strategy was clearly preferred by patients, even if patient groups were differentiated with respect to disability and disease duration, like in our study. However, increased depression correlated positively with the way of coping [33]. In that par-

ticular study, using the same test battery, female patients ($n = 207$) with comparable demographics like our study and a history of advanced MS (comparable to group 2 of the present study) scored for depressive coping 2.25 ± 0.9, for active coping 3.3 ± 1, for distracting coping 3.06 ± 0.9, for religious coping 2.89 ± 1 and for denying strategies 2.58 ± 1.2 [33]. Compared to patients with episodic tension-type headache from another study using the same coping test (FPI), comparable results as in MS patients were reported. However, female patients seemed to use more pessimistic coping strategies, regardless the type of chronic disease [37]. Although somatic symptoms of MS or side effects of steroid therapy (like influences on cognition, sleep or body weight) were excluded in our study as potential influence on mood and emotions, the influence of current immunomodulating therapies could not completely been ruled out. However, except for the subgroup of patients with EDSS of 0 being untreated, other patient groups were equally treated with immunomodulators and were not expected to be biased towards certain coping behaviour [19–22, 35]. Higher scores in complaints and insignificant mood rating in few but clearly disabled patients gave a hint of a yet high rate of compensation ability. Coping strategies might be shifted towards a more active side in patients who have less depression, regardless their current therapy, actual disability (EDSS) [21] or the kind of chronic diseases (rheumatoid arthritis, headache and cancer), but may rather depend on individual expectations [32, 33, 42]. With respect to depression this study supplemented and corroborated the findings regarding mood and depression of previous results [20]. In particular, EDS scores ≤ 1 seemed to be subject to certain variability, most likely due to limited sensitivity with regard to small changes of the test tools used, compared to healthy subjects. This hypothesis was supported by our data on follow-up of mood and cognitive functions, which showed insignificant fluctuations during 7 years of follow-up [22] with respect to mood changes but not to cognition. In contrary, cognitive deficits, in particular with respect to attention, visuoconstruction and working memory have clearly been correlated to disease duration, increased disability together with MRI visible lesions [1–3, 8, 9, 11, 12, 14, 23, 26, 28, 33, 34, 38–40, 45].

Our study showed early and continuously increasing neuropsychological deficits in a homogenous group of female MS patients. This supports the need for early therapeutic intervention based on the steadily increasing neuropsychological impairment as part of the chronic demyelinating process in MS. In addition, coping strategies did not seem to play an important role as co-factor but rather as independent psychological factor, depending on early diagnosis, expected prognosis, pharmacological treatment as well as on psychological training. Individual educational programs needed to improve the adjustment to the chronic disease. This could improve or at least stabilize the activities of daily living in these young patients, considerably [14, 23, 24, 27, 36, 44].

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