Immunotherapy Improves Cognitive Function in Secondary Progressive Multiple Sclerosis

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Introduction

Secondary progressive multiple sclerosis (SPMS) leads to an increase in physical disability. In addition, 43–70% of the patients with SPMS exhibit cognitive dysfunction, which predominantly affects language, visuospatial, and frontal-executive functions—such as attention, verbal fluency, and recall [1,2]. Despite the high prevalence of cognitive impairment, the impact of antiinflammatory treatment regimen on SPMS-related cognitive decline has rarely been studied.

This retrospective study investigates the influence of a first-time immunosuppressive therapy on cognitive function in SPMS. In addition, therapy- and MS-related factors predicting cognitive response during therapeutic immunosuppression are analyzed.

Methods

The ethics committee of Ruhr University Bochum approved the retrospective observational study. Since November 2007, 19 patients with SPMS who were treated *de novo* with mitoxantrone received between three and nine treatment cycles with intravenous mitoxantrone administration every 2–4 months leading to a cumulative dose of 48.1 ± 15.8 mg/m² (mean $\pm$ SD). Neuropsychological examination was performed before first treatment cycle and after 17 ± 7 months. Two of the 19 mitoxantrone-treated patients were reported in a preceding study [3]. Eleven patients with SPMS treated with intrathecal triamcinolone acetate (IT) served as controls. Patients received 21.6 ± 7.2 mg per

injection in 3–24 cycles, performed with an interval of 1–4 months. Two neuropsychological examinations were performed during IT treatment with an interval of 17 ± 14 months. All patients were identified by retrospective analysis of medical records. Neuropsychological examination was performed in a standardized manner as established at the Bochum center covering a broad range of cognitive domains using the following scales: Multiple-Choice Vocabulary Intelligence Test, German Performance Testing System Subtests 3 and 7, Regensburg Word Fluency Test subtest lexical word fluency and lexical category change, Verbal Learning and Memory Test A, Wechsler Memory Scale Subtests Visual Reproduction I and Digit Span Forward and Backward, and Shulman Clock Drawing Test. For evaluation of a confounding affective disorder, Beck Depression Inventory-II was performed with a threshold of >18 for clinical significant depression. At discretion of the evaluating neuropsychologists depending on coexisting disabilities and patient motivation, not every scale was carried out with every patient. Patients were defined as cognitively impaired if they scored at least 2 standard deviations below the average of healthy controls in at least one neuropsychological test. In addition, patients who had a score of 3 or higher in the Shulman Clock Drawing Test were diagnosed with cognitive impairment. The cutoff of 3 was chosen as Shulman et al [4]. showed that demented elderly had a mean score of 3, indicative of a relevant cognitive deterioration. Cognitive response was defined as improvement in $\geq 50\%$ of the performed tests at second neuropsychological examination. Statistical analyses were performed using SPSS.

Results

Baseline characteristics (gender, age at MS diagnosis, Expanded Disability Status Scale (EDSS), age at first neuropsychological examination), disease duration, time between longitudinal neuropsychological examinations, and comedication did not differ between groups. Also mean intravenous steroid dosages were equally distributed between the first and second neuropsychological examinations in each therapy group. In patients with SPMS in general as well as in both treatment subgroups, Beck Depression Inventory-II did not change over time (all $P > 0.05$) and clinically significant depression was not observed. Using the above-provided definition of cognitive impairment, 21 of 30 patients with SPMS demonstrated deficits at both time points. Most commonly affected tests were d2 (36%; 8/22), Regensburg Word Fluency Test subtest lexical category change (22%; 6/27), and German Performance Testing System Subtest 7 (20%; 5/25).

While IT-treated patients demonstrated no significant differences in neuropsychological function between the two assessments, mitoxantrone therapy led to a significant increase in five neuropsychological tests, which was almost >0.5 SD of healthy controls, and we observed a trend for improvement in another three subscales (Table 1). Between cognitive mitoxantrone responders ($n = 8$) and nonresponders ($n = 11$), EDSS at first assessment and presence of a mean leukocyte nadir $\leq 2000/\mu\text{L}$ were differently distributed (mean EDSS $\pm$ SD: nonresponders: 4.5 ± 1.4 versus responders:

5.9 ± 1.0 , $P < 0.05$; leukocyte nadir $\leq 2000/\mu\text{L}$ (responders 3/7 vs. nonresponders 0/10, $P = 0.02$; Figure 1).

Discussion

In this retrospective study, we compared longitudinal neuropsychological changes between patients with SPMS treated with mitoxantrone or IT. Remarkably, despite the short observation period of 17 months (mean), mitoxantrone-treated patients improved in five neuropsychological tests and we observed positive trends in additional three subscales, whereas the IT-treated group demonstrated no significant changes. Improvement was most pronounced in domains most commonly affected in patients with SPMS: attention (d2) and cognitive flexibility as a domain of executive function (Regensburg Word Fluency Test subtest lexical category change). This is in line with the previously identified "first dimension" cognitive deficits of patients with SPMS and patients with relapsing–remitting MS [1,2]. Additionally, in our mitoxantrone-treated group the performance in tests for the second dimension SPMS deficits (linguistic skills) improved [1,2]. The clinical relevance of our finding is supported by the fact that the observed increase was almost >0.5 SD of healthy controls. Comedication, baseline characteristics, and Beck Depression Inventory-II score were equally distributed; a confounding effect appears to be unlikely. The lack of cognitive deterioration of the IT group might be explained by the short observation period of

Table 1 Longitudinal change of neuropsychological test results within each therapy group (mitox vs. IT)

Neuropsychological tests	Mitoxantrone intravenous (mitox)			Corticosteroids intrathecal (IT)		
	n	Score change (mean $\pm$ SD)	P value (two-sided)	n	Score change (mean $\pm$ SD)	P value (two-sided)
MWTB	12	1.9 ± 2.1	0.02	7	-0.43 ± 2.5	0.69
Test d2—total processed characters	13	8.2 ± 81.3	0.35	9	-2.67 ± 62.5	1.00
Test d2—error ratio	13	-3.24 ± 8.28	0.03	9	0.54 ± 1.83	0.36
Test d2—total less false	13	18.1 ± 53.3	0.27	9	-5.7 ± 61.6	0.84
Test d2—concentration performance	13	12.7 ± 19.1	0.06[‡]	9	-3.0 ± 23.8	0.63
RWT—lexical word fluency	16	2.4 ± 3.6	0.02	11	0.6 ± 1.9	0.23
RWT—lexical category change	16	1.1 ± 2.8	0.19	11	-0.2 ± 3.5	0.98
VLMT—first repetition	18	-0.4 ± 1.9	0.39	11	-0.6 ± 1.9	0.28
VLMT—fifth repetition	18	1.1 ± 2.1	0.03	11	-0.5 ± 2.5	1.00
VLMT—interference	18	-0.6 ± 2.9	0.81	11	-0.6 ± 2.9	0.43
VLMT—retrieval after interference	18	1.1 ± 2.4	0.06[‡]	11	-0.6 ± 4.0	0.76
VLMT—retrieval after 30 min	18	0.5 ± 3.4	0.57	11	-0.3 ± 2.3	0.59
VLMT—recognition less false	17	-0.1 ± 4.0	0.78	7	-5.1 ± 6.4	0.13
WMS-R—digit span forward—Score	18	0.7 ± 1.2	0.04	10	-0.7 ± 1.4	1.00
WMS-R—digit span forward—Digits	18	0.5 ± 0.9	0.06[‡]	10	-0.2 ± 0.8	1.00
WMS-R—digit span backward—Score	18	-0.3 ± 1.8	0.68	10	0.2 ± 2.0	0.25
WMS-R—digit span backward—Digits	18	-0.2 ± 1.0	0.41	10	0.1 ± 0.9	0.75
WMS-R—visual reproduction I	12	-0.8 ± 2.8	0.32	6	-3.5 ± 8.4	0.63
GPTS—Subtest 3	15	-0.1 ± 3.1	0.92	9	2.9 ± 3.4	0.06 [‡]
GPTS—Subtest 7	15	0.3 ± 3.2	0.97	9	2.1 ± 7.5	0.45
Shulman Clock Drawing Test	19	-0.1 ± 0.9	0.91	11	-0.1 ± 0.8	1.00

Statistic: Wilcoxon signed-rank test. n = number of patients tested at both assessments. MWTB, Multiple-Choice Vocabulary Intelligence Test; RWT, Regensburg Word Fluency Test; VLMT, Verbal Learning and Memory Test; WMS-R, Wechsler Memory Scale-Revised; GPTS, German Performance Testing System. Tests with $P < 0.1$, which indicates an improvement of cognitive changes in mitoxantrone treated patients, are marked in bold. [‡]Observed significance in one-tailed test (P (each test) = 0.03).

Figure 1 Predicting factors of cognitive response to mitox therapy in patients with SPMS. Left: EDSS at initiation of therapy. Responders show a significantly higher EDSS (Mann–Whitney test). “O” represents an outlier. Right: Mean leukocyte nadir after mitox infusions. A significantly higher number of responders were below the leukocyte cutoff of 2000 leukocytes/ μL (chi-square test).

17 months between the first and second neuropsychological examinations. This is in line with other studies [5–7]. These studies investigating in total 142 patients with progressive MS did not find a cognitive deterioration within an observation period of 12 and 24 months [5–7]. In our analysis, a higher EDSS at initiation of mitoxantrone and a lower leukocyte nadir (cutoff ≤ 2000 leukocytes/ μL) during therapy were associated with cognitive response. We decided to use this leukocyte cutoff, because it was previously suggested to use a mitoxantrone treatment regimen, which has the potential to induce leukopenia (below 2000 leukocytes/ μL) as indication for an immunosuppressive state [8]. An even lower cutoff was ruled out due to safety reasons [9]. Thus, the lower leukocyte nadir in mitoxantrone responders provides an immunological rationale for the observed clinical effects on cognition. This might be caused by mitoxantrone-mediated mechanisms targeting inflammatory processes in the central nervous system in patients with SPMS [10]. A previous study reported stability of neuropsychological function under mitoxantrone when analyzing percentile ranks after an observation period of 24 months [3]. This discrepancy may be related to study design and inclusion criteria: in our study, the second neuropsychological examination was performed within 4 months after the last infusion of mitoxantrone (preceding study of Schroeder et al.: between 8 and 12 months), and mitoxantrone-pretreated patients were excluded in our analysis [3].

Limitations of our study are the retrospective design, the lack of more objective paraclinical outcome data, such as MRI scans, and the overall small study cohort, which might have influenced some

effects (e.g., leukocyte nadir) in our observation. Our definition of cognitive impairment is stricter than the definition used in other studies [7,8]. The main aim of this more rigorous classification of cognitive impairment was the attempt to avoid overestimation. However, comparability with other studies is limited as standardization of cognitive testing in general is poor and our test battery may have flaws and limitations likewise. Nevertheless, as our cohort demonstrated a typical pattern of cognitive impairment in SPMS [2], our study population seems to be representative of cognitive deficits during the progressive phase of MS. Thus, our data highlight the potential impact of immunosuppression on cognition and particularly emphasize the role of neuroinflammation on neurodegeneration in SPMS [10]. As a consequence, immunosuppressive therapy may still be a valid treatment option in SPMS patients with marked cognitive impairment and high EDSS. Larger studies with a prospective design are necessary to validate our findings.

Conflict of Interest

M. Kinner reports no disclosures. R. Hoepner received research and travel grants from Biogen and travel grants from Novartis. P. Klotz reports no disclosures. C. Prehn reports no disclosures. S. Faissner received travel grants from Biogen and Genzyme. A. Salmen received personal compensation for activities with Novartis, Sanofi and Almirall Hermal GmbH. R.A. Linker received personal compensation as a speaker or consultant for Bayer, Biogen, Genzyme, Merck, Sanofi-Aventis, Roche and Teva. R.A. Linker

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Supporting Information

The following supplementary material is available for this article:

Table S1. Baseline variables of included patient groups.