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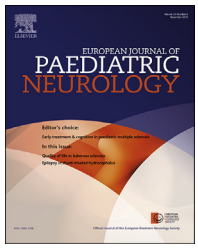

Original article

Early effective treatment may protect from cognitive decline in paediatric multiple sclerosis

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ABSTRACT

Background: Cognitive impairment (CI) is a critical feature for patients with childhood or juvenile multiple sclerosis (MS).
Objective: To promote the understanding of CI and to address the impact of different pharmacological treatment strategies on cognitive performance in this patient group.
Methods: A cohort of 19 patients with therapy-naïve or ß-Interferon-treated juvenile MS completed a comprehensive neuropsychological assessment at initial presentation (baseline) and on average 2.5 years later (follow-up). The assessments were complemented with a neuropaediatric examination and conventional cerebral magnetic resonance imaging (MRI).
Results: 9 patients (47%) were impaired in at least one test at baseline (z-score <-1.645 compared with age-adjusted normative data), with the highest impairment frequency in the domains processing speed and attention & executive functions. At follow-up a higher impairment frequency was prominent in those patients whose therapy had not been escalated (N = 13, 69% impaired in at least one test), while cognition was preserved or ameliorated in patients whose treatment had been escalated to highly effective drugs (N = 6, 0% impaired) during the observational period. These group differences at follow-up were not attributable to differences regarding demographics, MRI metrics or cognitive performance at baseline.
Conclusion: Our findings confirm that paediatric MS is associated with considerable CI already in early disease stages. Early administration of highly effective treatment may

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protect from cognitive decline or alleviate CI in juvenile MS, but larger controlled trials are warranted to confirm these preliminary results.

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) commonly diagnosed in young adults. According to published data, approximately 5–7% of all patients are newly diagnosed with MS before the age of 18.[1] The incidence of juvenile MS in Germany has been estimated as 0.64 per 100.000 person-years.[2]

MS can cause both cognitive and physical disability.[3] While in adult patients cognitive impairment (CI) is a well-defined and established characteristic of MS,[4] data on CI in paediatric MS is more limited, partly because assessment and interpretation of cognitive performance is clinically challenging in a context of ongoing neurological and neurocognitive maturation.[5,6] Nevertheless, a range of studies have been conducted in the last decade, providing evidence for a considerable degree of CI in paediatric and juvenile patients with MS.[7–12] Using diverse neuropsychological tests and varying definitions of CI, earlier cross-sectional studies have reported a CI incidence rate between 29.4% and 35% for paediatric MS patients.[7–12] Even in children with clinically isolated syndrome (CIS) – defined as a preliminary stage of MS – CI is apparent in approximately 20% of all established cases[10,13,14] and its occurrence may be a predictor for further MS development.[15]

Similar to adult patients, paediatric MS patients' deficits were found in a range of cognitive domains including episodic memory, visuomotor integration and particularly processing speed and executive functions.[7,10,12,16] However, the relationship between CI, motor function, Expanded Disability Status Scale (EDSS) and number of relapses is controversial.[3,8] For example, MacAllister and colleagues and Julian and colleagues found a strong correlation between CI and EDSS scores,[8,10] whereas in another multicenter study EDSS scores and the number of relapses were not systematically associated with the presence or severity of CI in children.[11]

Undoubtedly, CI is a particularly critical feature of paediatric MS since cognitive abilities may determine a child's future professional career as well as its personal wellbeing. Different neuronal resources (e.g. brain plasticity, maturation of the CNS), parental setting and acquired compensatory strategies are assumed to influence cognitive performance and the course of CI in paediatric MS.[11,12] Moreover, influences of psychological factors such as mood, fatigue and anxiety on cognition have been well documented in paediatric MS and may mediate cognitive test performance.[5] To date though, we are not able to differentiate patient characteristics in order to use them to explain the different results in cognitive functioning between patients, or to predict or consequently alter the course of CI. For adult MS patients a promising effect on cognition has been shown for first-line platform therapies (e.g., interferon beta-1a, glatiramer acetate, dimethyl fumarate)[17,18] and particularly for escalation therapies (e.g., alemtuzumab, natalizumab, fingolimod).[19–21] While efficacy and safety of different disease-modifying drugs (DMDs) to avoid relapses and accumulation of lesions on MRI was previously demonstrated in paediatric MS,[22–24] the impact of these different types of DMDs on cognition is not known so far.

In this longitudinal observational cohort study, we thus assessed neurocognitive functions and the clinical and MRI features in newly diagnosed paediatric MS patients and compared the longitudinal changes in CI between patients that received platform therapy and those that were escalated on highly efficient DMDs. The main study goals were to collect data on the degree and progression of CI and to explore the impact of high-efficacy escalation therapies on the longitudinal course of CI in childhood and juvenile MS.

2. Material and methods

2.1. *Participants*

Nineteen paediatric patients (14 female, 5 male; mean age 15.05 years, age range 10–17 years) were recruited in the Neuropaediatric Department of the University Hospital Münster, and were prospectively followed-up between April 2012 and May 2017. The inclusion criteria were: (i) a recent diagnosis of definite MS according to the 2010 revised McDonald criteria[25] and revised criteria for paediatric multiple sclerosis and immune-mediated CNS demyelinating disorders,[26] (ii) either no treatment (therapy-naïve) or platform (interferon beta-1a, glatiramer acetate, dimethyl fumarate) therapy, (iii) age <18 years at baseline assessment, and (iv) the absence of comorbid neurologic and psychiatric diseases (including major depression) known to interfere with cognitive functioning. Patients were selected either via outpatient care in our neuropaediatric department or within in-patient stay on our neuropaediatric ward. Hereby it was ensured that all eligible patients, who agreed, were included within the study and selection bias was reduced to a minimum level. Clinical examination, structural MRI, and neuropsychological assessment were performed at baseline and again at follow-up, which on average took place 2.5 years later. For each assessment, we ensured a minimum interval of 30 days since the last treatment with cortisone due to its known effects on cognitive performance. The study was approved by the local ethics committee (Reference numbers: 2012-310-b-S; 2015-

176-f-S). Parents signed the informed consent forms on behalf of minor patients.

2.2. Clinical examination and MRI

Physical disability was scored by a trained rater (CE) using the EDSS.[27] Structural cerebral MR images were obtained by different MRI scanners with either 1.5 or 3 T. MRI included diverse prior and post gadolinium sequences. Lesion load was manually determined by considering all available sequences. Volumetric information from different brain areas (hippocampus, thalamus and total cortex) were analysed (for available 3 T T1 3-D sequences) by using the SurferMagix Module by BrainMagix, Version 2.0.1. (Imagilys, Brussels, Belgium).

2.3. Neuropsychological assessment

Administration and scoring of all cognitive tests were carried out by trained neuropsychologists blinded to medication status of patients. A comprehensive neuropsychological test battery was administered focussing on tests previously validated in paediatric samples (see supplementary table s1 for details on the used normative data for both baseline and follow-up). Single tests and outcomes were condensed into four cognitive domains: *verbal learning & memory; visuoconstruction & visual memory; processing speed; attention & executive functions*. If available, parallel test versions were used at follow-up to account for any practice effects (e.g., for the Rey Auditory Verbal Learning Test (RAVLT) and the Rey Complex Figure Test (RCFT)).

Raw test scores were transformed into normative z-scores, and stratified for the patient's age, sex and educational years. In cases when normative data for specific ages were not available, the nearest available age (or age ranges) from the respective normative sample data was used. Performance below a normative z-score of −1.645 (corresponding to the 5th percentile rank of the normative sample) was classified as "impaired" performance. The number of impaired test performances was computed for each patient at baseline and follow-up as the main outcome.

For a more detailed analysis of longitudinal changes in the four cognitive domains we further calculated a cognitive impairment index (CII), similar to the procedure put forth by Amato and colleagues,[12,28] but using more conservative cut-off scores to define impairment: For each test parameter a score of 0 was assigned if performance was above a normative z-score of −1.28 (i.e., above the 10th percentile rank). A score of 1 was assigned if the test performance was between $z = -1.28$ and $z = -1.645$ (i.e., between the 10th and 5th percentile rank) and a score of 2 was assigned for performances between $z < -1.645$ and $z = -2.326$ (i.e., between the 5th and 1st percentile rank). For performances below $z = -2.326$ (i.e., below the 1st percentile rank) a score of 3 was assigned, indicating the largest possible CII. This procedure was repeated for each test and each patient at baseline and at follow-up, resulting in sums of CII for each cognitive domain and test parameter that reflect the respective individual impairments.

To measure health-related quality of life as a potential influence of cognitive performance, the Pediatric Quality of Life Inventory (PEDS-QL)[29] scales were given to both patients and their parents. Here, the summary score for psychosocial health was analysed, involving reports on emotional functioning, social functioning and school functioning.

2.4. Statistical analyses

IBM SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used for data preparation and statistical analyses. Additionally, GraphPad Prism (V 7.0a) was used to create figures. Data was examined for normality and skewness prior to analyses. Descriptive statistics were computed for baseline demographics, clinical scores, MRI and cognitive characteristics. The number of impaired cognitive tests ($z < -1.645$), the overall sum of CII, the sum of CII for each cognitive domain, and the longitudinal changes in CII (delta) were compared between the two groups (treatment escalated vs. non-escalated) using two-sided non-parametric Mann–Whitney U-tests. To ensure that groups were parallel with regard to potentially confounding influences, the differences in demographics, clinical scores involving reports on psychosocial health as well as MRI data were compared between the two treatment groups in a similar manner using Mann–Whitney U-tests, for both baseline and follow-up data. An alpha-level of .05 was employed to flag statistical significance for all tests.

3. Results

3.1. Baseline

Baseline demographics, clinical and paraclinical characteristics of the total paediatric MS sample are summarized in Table 1. Although patients showed minor physical disability (mean EDSS = 0.5), a considerable total number of relapses (mean = 2.68) and a substantial lesion load depicted through MRI (mean number of lesions = 21.44) were revealed – particularly when considering the relatively short average disease duration (mean = 12.95 months). Patients were either therapy-naïve (N = 3) or received interferon beta-1a (N = 16) at

Table 1 – Baseline sample characteristics of the n = 19 paediatric MS patients.

Demographics	Mean (SD)	
Age (years)	15.05 (2.01)	
Sex (f/m)	14/5	
Education (years)	9.73 (1.52)	
Clinical and Paraclinical Measures	**Mean (SD)**	**Median (IQR)**
Disease Duration (months)	12.95 (23.52)	4.00 (9.00)
EDSS	0.50 (0.61)	0.00 (1.00)
Total Number of Relapses	2.68 (1.88)	2.00 (1.00)
Number of Lesions on MRI	21.44 (17.52)	15.50 (27.75)
Treatment		
Naïve, n	3	
Interferon beta-1a, n	16	

Note. EDSS = Expanded Disability Status Scale; Disease Duration = time since first symptoms; IQR=Interquartile range.

baseline. Baseline cognitive test performances of the sample are shown in Table 2. In total, 9 out of 19 patients were impaired in at least one parameter of the neuropsychological test battery, indicating an overall moderate incidence of CI. CI occurred most often in the domains *processing speed* (4/19 patients with at least one failed test; sum of CII = 12) and *attention & executive functions* (7/19 patients with at least one failed test; sum of CII = 24), whereas the domains *verbal learning & memory* and *visuoconstruction & visual memory* were comparatively preserved. The most frequently impaired single test parameters were the Trail Making Test (TMT) part A and part B, again indicating the most prominent impairment in cognitive processing speed and set-shifting abilities.

3.2. *Follow-up*

The average time interval between baseline and follow-up assessment was approximately 2.5 years (29.1 months, range 6–53 months). At follow-up, the treatment of six patients had been escalated to a high-efficacy DMD (N = 3 Natalizumab; N = 3 Fingolimod) and the remaining thirteen patients were still on a first-line platform therapy (N = 10 β-Interferon, N = 2 Dimethyl fumarate, N = 1 Glatiramer acetate). Escalation of treatment was initiated based on individual decisions and unrelated to cognitive status (see supplementary table s2 for details). Number of relapses was higher in the treatment escalated group vs. the non-escalated group at follow-up indicating a more active disease course, U = 58, p = .041 (see supplementary table s3 for details on all other clinical and paraclinical scores at baseline and follow-up). The average treatment duration of the escalated patients until follow-up assessment amounted to 10 months.

3.2.1. *Differential cognitive performances at follow-up assessment*

Table 3 depicts the differential cognitive performances of the treatment escalated (N = 6) and non-escalated group (N = 13) at follow-up. Patients whose therapy had not been escalated within the observational period after baseline assessment showed a significantly higher number of impaired test parameters at follow-up than those patients with escalated therapies, U = 12, p = .017 despite the higher disease activity in the escalated group. More specifically, employing a conservative cut-off at a z-score below −1.645 resulted in no patients in the escalated group being impaired at follow-up for any of the cognitive test parameters albeit four of these patients had failed in at least one test parameter at baseline, indicating cognitive amelioration in the escalated group (Fig. 1A). Critically, there were no significant differences between the groups at baseline regarding both, the number of impaired tests, U = 51, p = .323 or the sum of CII, U = 41, p = .898 (supplementary table s4). In the more fine-grained analysis of the CII a similar pattern was observed showing a significantly lower overall CII at follow-up for the escalated group, U = 15.5, p = .036 (Fig. 1B). Visual exploration of the CII across the four different cognitive domains revealed that this pattern was similar in each of the four cognitive domains, however, between-group comparisons for the separate domains failed to reach statistical significance, indicating no domain-specific differences between escalated and non-escalated patients.

Table 2 – Baseline results of the cognitive assessment in the sample of n = 19 paediatric patients.

Cognitive Domain	Mean (SD)	Number of impaired tests (z < −1.645)	Sum of CII
Overall Cognition (all test parameters)		9/19[a]	53
Verbal Learning & Memory		2	10
RAVLT 1-5	60.32 (8.93)	0	2
RAVLT 6	12.26 (3.17)	1	5
RAVLT 7	13.11 (2.40)	1	3
RAVLT 8	13.71 (1.89)	0	0
Visuoconstruction & Visual Memory		2	7
RCFT Copy Accuracy	33.15 (2.74)	2	5
RCFT 3 Minute Free Recall Accuracy	21.80 (5.41)	0	2
Processing Speed		4	12
TMT-A	25.92 (7.93)	3	9
SDMT	56.23 (13.71)	0	0
RCFT Time to Copy (sec.)	272.35 (150.39)	1	3
Attention & Executive Functions		7	24
Digit Span forwards	7.52 (1.71)	0	1
Digit Span backwards	6.47 (1.54)	1	2
Corsi Block-Tapping test forwards	9.53 (2.50)	1	3
Corsi Block-Tapping test backwards	8.80 (1.74)	0	1
Phon. Fluency	12.94 (4.89)	0	2
Sem. Fluency	23.10 (6.76)	1	4
TMT-B	66.94 (17.68)	4	11

Note. [a] Nine out of the 19 patients had at least one impaired test performance. CII= Cognitive Impairment Index; A higher sum of CII represents a relative larger average impairment in the respective test or cognitive domain. RAVLT = Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; TMT-A = Trail Making Test part A; SDMT= Symbol Digit Modalities Test (written); TMT-B = Trail Making Test part B; Phon. Fluency = Phonematic verbal fluency with letter S (1 min.); Sem. fluency = Semantic verbal fluency with animals (1 min.).

Table 3 – Follow-up of differential performances in cognitive test parameters and domains for the treatment escalated (n = 6) vs. non-escalated (n = 13) paediatric MS patient groups.

Cognitive Domain	Mean (SD)		Number of impaired tests (z <-1.645)		Sum of CII		p-values
	Non-Escalated	Escalated	Non-Escalated	Escalated	Non-Escalated	Escalated	
Overall Cognition (all test parameters)			9/13[a]	0/6[a]	41	7	.036*
Verbal Learning & Memory			3	0	8	0	.467
RAVLT 1-5	59.85 (10.37)	64.33 (6.05)	1	0	2	0	
RAVLT 6	13.00 (3.24)	13.33 (1.03)	1	0	3	0	
RAVLT 7	12.61 (3.04)	13.83 (0.98)	1	0	2	0	
RAVLT 8	13.69 (1.54)	15.00 (0.00)	0	0	1	0	
Visuoconstruction & Visual Memory			1	0	4	0	.437
RCFT Copy Accuracy	33.69 (2.42)	35.50 (0.83)	1	0	4	0	
RCFT 3 Minute Free Recall Accuracy	26.76 (5.35)	25.33 (3.98)	0	0	0	0	
Processing Speed			4	0	11	2	.467
TMT-A	25.56 (7.15)	21.66 (7.08)	2	0	5	1	
SDMT	54.92 (11.21)	58.60 (13.18)	1	0	3	1	
RCFT Time to Copy (sec.)	227.3 (119.93)	164.60 (75.53)	1	0	3	0	
Attention & Executive Functions			4	0	18	5	.521
Digit Span forwards	7.15 (1.57)	8.50 (2.07)	0	0	2	0	
Digit Span backwards	6.53 (1.05)	8.83 (2.22)	0	0	0	0	
Corsi Block-Tapping forwards	9.17 (2.25)	8.75 (3.77)	0	0	0	1	
Corsi Block-Tapping backwards	8.25 (1.76)	8.25 (1.70)	0	0	2	1	
Phon. Fluency	13.38 (5.22)	14.66 (2.58)	1	0	4	0	
Sem. Fluency	22.30 (8.26)	20.33 (8.06)	0	0	4	3	
TMT-B	60.53 (13.95)	46.80 (15.72)	3	0	6	0	

Note. [a] = Nine out of the 13 non-escalated patients and none out of the six escalated patients had at least one impaired test performance. * = significant at p = .05; p-values relate to Mann-Whitney-U tests comparing Sum of CII in non-escalated vs. escalated patients. CII=Cognitive Impairment Index; A higher sum of CII represents a relative larger average impairment in the respective test or cognitive domain. RAVLT = Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; TMT-A = Trail Making Test part A; SDMT=Symbol Digit Modalities Test (written); TMT-B = Trail Making Test part B; Phon. Fluency = Phonematic verbal fluency with letter S (1 min.); Sem. Fluency = Semantic verbal fluency with animals (1 min.); p-values indicate between-group differences regarding CII at follow-up derived from non-parametric Mann-Whitney-U Tests.

3.2.2. *Differential longitudinal changes between baseline and follow-up*

Between-group differences regarding the longitudinal changes from baseline to follow-up in the CII are depicted in Fig. 1C. A larger longitudinal improvement in overall CII was visible for escalated patients compared to non-escalated patients, although this effect failed to reach statistical significance, U = 18.0, p = .072. Likewise, no significant between-group differences regarding the change of CII emerged for any of the four cognitive domains separately. Visual exploration however, again showed that longitudinal changes in CII were negative (i.e., lower CII at follow-up compared to baseline) throughout all cognitive domains for the escalated group. Conversely, patients that had not been escalated to a high-efficacy DMD were either unchanged or had a higher CII in all of the four cognitive domains at follow-up compared to baseline (Fig. 1C). Comparisons of all clinical and paraclinical characteristics of the treatment escalated vs. non-escalated groups can be found in supplementary table s3. There were no significant between-group differences regarding either demographics, clinical parameters (including EDSS and PEDS-QL psychosocial health summary) or MRI parameters (including brain volumetric analyses of the cortex, the thalamus and the hippocampus) that could directly explain the divergent cognitive performances of the escalated patients at follow-up (Mann–Whitney U-tests comparing demographics, and clinical and MRI parameters at follow-up and baseline: all p-values>.05; see supplementary table s3 for details).

4. Discussion

CI is a critical feature for patients suffering from paediatric MS since cognitive ability may determine a child's future private and professional wellbeing. The present cohort study explored longitudinal progression and potential influences of treatment on cognitive performance changes in children and adolescents suffering from MS. In line with previous studies,[7–12] paediatric MS patients in our cohort showed pronounced CI already at baseline shortly after first diagnosis: 47% of patients demonstrated CI at baseline by impaired performance in at least one standardized neuropsychological

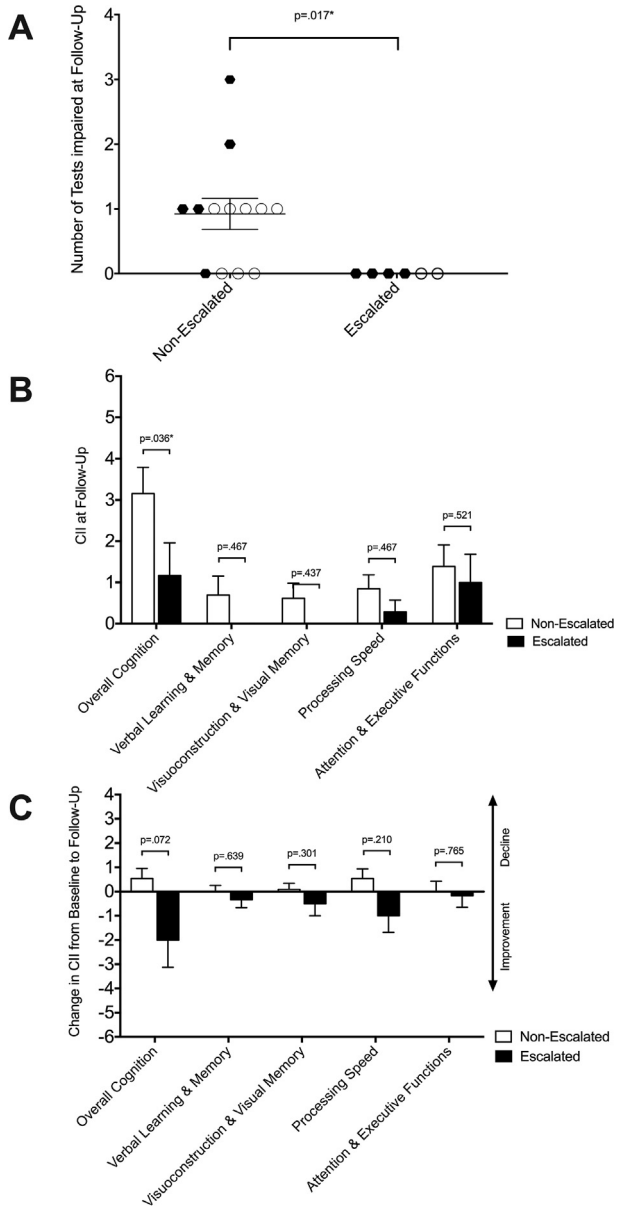

Fig. 1 – A) Number of impaired tests ($z < -1.645$) at follow-up for the non-escalated vs. escalated patients separately. Black diamond-shaped cases represent cases that were impaired in at least one test at baseline, whereas circles represent cases without impaired tests at baseline. B) Mean sum of the Cognitive Impairment Index (CII) overall (all test parameters) and for each neuropsychological domain separately at follow-up. Larger CII represent more cognitive impairment (CI). C) Mean change between baseline and follow-up in the sum of CII overall (all test parameters) and for each neuropsychological domain for escalated vs. non-escalated patients. Negative values indicate a lower CII at follow-up compared to baseline, indicating alleviation of CI.

test. We defined a test performance as "impaired" if it was −1.645 standard deviations below the normative mean of the respective age-group. For a more detailed analysis of CI we also computed cognitive impairment indices (CII), based on deviations of the performances from the normative sample data. Employing a comparable methodology,[12,28] similar numbers regarding the frequency of CI in paediatric MS were already described earlier. Also in line with previous studies, the highest frequency of deficits were found for the domains *processing speed* and *attention & executive function*.[9–12,14,16]

To date, information on the progression of CI in paediatric MS is still limited and controversial: The rate of longitudinal cognitive decline varies between 3.8% and 75% in different longitudinal studies.[8,9,14,30,31] One of the largest multicenter cohort study involving 48 patients reports a cognitive decline in 56% of patients at a follow-up assessment five years after baseline although a substantial proportion of patients also improved longitudinally.[12] Importantly, one has to take into account that the employed neuropsychological tests, the used normative data, the respective definitions of CI and the duration of follow-up strongly differ between the available studies. Across studies however, younger age at disease onset seems to be associated with a greater risk of developing cognitive decline in the future.[32,33] Previous studies have furthermore emphasized the important influences of psychosocial wellbeing, fatigue, anxiety and affective disorders on the measurement of CI in paediatric patients in MS.[5,12,34]

For adults, several studies have previously provided evidence that high-efficacy escalation DMDs may stabilize cognitive outcome in MS.[19–21] However, for paediatric MS patients, studies focussing on this aspect are missing so far and the potential influence of different treatments has not been investigated in depth in previous studies.[12,30,35,36] In the here described cohort, the treatment of six patients had been escalated to a more potent escalation DMD (natalizumab or fingolimod) during the observation period owing to higher relapse rates in these patients. Interestingly, cognitive performance remained preserved or ameliorated in these patients, while deteriorating cognitive performance was prominent in those patients who remained in first-line platform therapy (β-interferon or glatiramer acetate). Employing the aforementioned cut-off criterion resulted in no patient in the escalated group being impaired at follow-up for any of the cognitive test parameters. Although larger controlled drug trials are needed, these findings provide preliminary evidence that highly potent DMDs might protect from cognitive decline and reduce CI in childhood and juvenile MS. In our sample, demographics, duration of disease, EDSS scores, self-reports and parent-reports on psychosocial health as well as MRI parameters did not differ significantly between treatment escalated vs. non-escalated patients at either baseline or follow-up, suggesting that the divergent courses of CI were not simply due to group-differences or changes regarding these parameters. Thus, the improvement of overall cognition cannot be explained by improvement or stabilization of general clinical and paraclinical parameters in the escalated group. Furthermore, the number of relapses was even higher in the treatment escalated group during the observation period reflecting a more active disease phenotype.

Our results highlight the importance to assess cognitive performance in paediatric patients with MS as results may be independent from other commonly used proxies for disease severity.[37] Previous studies investigating the association of CI and general disease severity markers in patients with

paediatric MS have yielded heterogeneous results.[3,8] Clinical variables, such as the number of relapses and EDSS, strongly correlate with CI in two studies,[8,10] whereas another multicenter study revealed no association of CI with EDSS scores and the number of relapses.[11] One potential explanation for these diverging results is the individual extent of compensatory capacities (e.g., cognitive reserve, environmental enrichment), which is particularly variable in younger patients with a low disease burden. Such variations may thus mediate or cloud the relationship between physical disability, MRI metrics and CI in MS.[38] Regarding structural MRI metrics and cognition in childhood MS several studies have failed to find consistent associations, whereas interindividual differences in functional brain activation patterns have been found more consistently.[39,40]

A range of methodological limitations have to be considered for our study: First, the present study is limited by a small sample size and may be underpowered to detect clinically relevant differences regarding clinical and paraclinical markers that predict or determine cognitive status or decline in paediatric MS. Furthermore, our treatment groups were not randomized, as is otherwise common in clinical studies, but instead based on individual treatment decisions albeit unrelated to cognitive performance or subjective cognitive complaints. Owing to the observational nature of our study, extrapolation of our results may also be hampered by the large heterogeneity regarding observation- and treatment periods again emphasizing the need for controlled multicenter drug trials of larger scales. Despite these limitations, the potential success of treating CI in childhood MS with highly effective escalation DMDs may be evident from our results.

In conclusion, we find that patients with highly effective escalation therapies show reduced CI at follow-up, and even improve in overall cognitive functioning despite developing more clinical relapses within the observation period. Cognitive performance may be unconnected to changes in typical clinical markers in paediatric MS, emphasizing the need for standardized cognitive testing as an important marker of disease burden.[37] In order to validate our findings of the potential positive effects of second-line escalation DMDs on cognition in paediatric MS, large-scale randomized and placebo-controlled multicenter clinical trials – also assessing safety and side-effects – are urgently needed.

Conflicts of interest

AJ received honoraria for acting as a speaker for Actelion Pharmaceuticals unrelated to this work. CE received honoria for lecturing and travel expenses for attending meetings from Bayer Health Care; Novartis Deutschland GmbH; Actelion Pharmaceuticals Ltd., Merck Serono GmbH, Biogen MA Inc. ER, HL, PP, N-CL, HO and KG report no disclosures. JK received honoraria for lecturing from Biogen, Novartis, Mylan and Teva, and financial research support from Sanofi Genzyme. HW is acting as a paid consultant for Abbvie, Actelion, Biogen, IGES, Novartis, Roche, Sanofi-Genzyme, and the Swiss Multiple Sclerosis Society. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgesellschaft (DFG), Else Kröner Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Münster and RE Children's Foundation, Biogen GmbH, GlaxoSmithKline GmbH, Roche Pharma AG, Sanofi-Genzyme. SGM receives honoraria for lecturing, and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Münster, German Foundation Neurology and Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, Merck Serono, Novartis, ONO Pharma, Roche, and Teva.

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Appendix A. Supplementary data

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