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Childhood multiple sclerosis is associated with reduced brain volumes at first clinical presentation and brain growth failure

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Abstract

Background: Paediatric multiple sclerosis (pedMS) patients at a single site were shown to have reduced brain volumes and failure of age-expected brain growth compared to healthy controls. However, the precise time of onset of brain volume loss remains unclear.

Objective: To longitudinally study brain volumes in a multi-centre European cohort at first presentation and after 2 years.

Methods: Brain volumes of high-resolution magnetic resonance imaging (MRI) data from 37 pedMS patients at first presentation prior to steroid therapy and at 2-year follow-up ($n=21$) were compared to matched longitudinal MRI data from the NIH Paediatric MRI Data Repository.

Results: Patients showed significantly reduced whole brain, grey and white matter and increased ventricular volumes at initial presentation and at follow-up compared to controls. Over 2 years, patients exhibited significant reduction of whole brain and white matter volumes, accompanied by increased ventricular volume. Brain volume loss at follow-up correlated with a higher number of infratentorial lesions, relapses and an increased Expanded Disability Status Scale (EDSS) score.

Conclusions: In pedMS patients, brain volume loss is present already at first clinical presentation and accelerated over 2 years. Increased disease activity is associated with more severe brain volume loss. MRI brain volume change might serve as an outcome parameter in future prospective pedMS studies.

Keywords: Paediatric multiple sclerosis, magnetic resonance volumetry, brain growth, disease-modifying therapies

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Introduction

In recent years, important progress has been made in the field of paediatric multiple sclerosis (pedMS) thereby identifying characteristic clinical and imaging features of the disease in childhood. Compared to adult-onset MS, pedMS is characterized by an increased relapse rate and a higher magnetic resonance imaging (MRI) activity with more T2/FLAIR and gadolinium-enhancing lesions in the initial phase of the disease.[1–3] In comparison to adult MS, pedMS therefore seems to be associated with an increased disease activity, but also with a higher potential for recovery. This is indirectly supported by the observation that disability progression is slower and time to secondary progression is longer in pedMS.[4] However, children with MS experience significant disability at a younger age and adults previously diagnosed with pedMS suffer from more pronounced cognitive impairment compared to adult-onset MS patients, even when adjusted for disease duration.[5]

These observations are in line with recent imaging studies showing reduced whole brain and thalamus volumes and failure of expected brain growth in pedMS patients during adolescence.[6,7] In these two studies, MRI scans were obtained 3 years (mean 3.1, range 0.2–13.5 years) after first attack and within the first year after first attack (mean 1.17, range 0–4.7 years),

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respectively. Baseline scans (at first attack) were excluded in these studies as corticosteroids were often administered at that time (i.e. to avoid confound by pseudoatrophy). Importantly, these studies showed that pedMS patients at these early disease stages already show reduced brain volume compared to healthy controls.[7] However, whether brain volume in patients with pedMS is reduced already at first clinical presentation prior to first (steroid) treatment remains unclear.

Here, we systematically assessed brain volume in a European cohort of children with pedMS at their first clinical presentation, prior to intravenous methylprednisolone treatment. In addition, longitudinal brain volume development was evaluated over 2 years compared to a large cohort of healthy children. Number of relapses, T2 lesion load and standard disease-modifying therapies (DMTs) commonly applied in pedMS were linked to brain volume loss over time.

Patients and methods

Patients

Patients were recruited at seven different hospitals in Germany and Austria (Children's Hospital Datteln, Witten/Herdecke University, Datteln, Germany; Olgahospital, Stuttgart, Germany; Medical University of Vienna, Austria; Dr von Hauner Children's Hospital, Ludwig Maximilian University of Munich, Germany; Children's Hospital Augsburg, Germany; Children's Hospital, Medical University of Innsbruck, Innsbruck, Austria; University Children's Hospital, Heinrich-Heine-University, Düsseldorf, Germany). Inclusion criteria were diagnosis of pedMS according to the criteria of the International Paediatric Multiple Sclerosis Study Group (IPMSSG);[8] cerebral MRI including MPRAGE, FLAIR and/or T2-sequences at first clinical presentation; clinical follow-up of at least 2 years and availability of clinical details such as number of relapses, Expanded Disability Status Scale (EDSS) score and applied DMTs.

A total of 37 patients were included in the study with a median age of 15 years (range 10–17 years) at first clinical presentation (18 females; 48.6%). Detailed demographic data are provided in Table 1. Oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) were detected in 31 patients (83.8%), and the median CSF cell count was 7.5 cells/μL (range: 0–52 cells/μL). Sixteen patients had no high-resolution MRI data acquired at the 2-year follow-up and were therefore excluded from MRI follow-up analysis. Patients had a median of two relapses (range 1–5) within the first 2 years and a median EDSS score of 0 (range 0–2) at follow-up after 2 years. Of the 21 patients included in follow-up analysis, DMTs were given to 13 patients (61.9%) within the first 2 years. Of this cohort, 10 children received interferon beta (two escalated to natalizumab and one switched to glatiramer acetate) and 3 children were administered monthly intravenously natalizumab without previous first-line therapy. The study was approved by the Ethics Committee of the University Witten/Herdecke, Germany, and all caregivers gave informed consent.

MRI data acquisition and analysis

Baseline MRI was performed at first clinical presentation prior to application of intravenous methylprednisolone. At follow-up (study design illustrated in Supplemental Figure 1), high-resolution MPRAGE sequences were available for 21/37 patients (same scanner in most patients; exclusion of seven patients with different scanner for follow-up MRI showed no difference in results; Supplemental Figure 2). None of the patients had received steroid treatment within 1 month prior to follow-up MRI scan. Mean time between first and follow-up MRI was 24.7 ± 6.8 months.

High-resolution MRI scans (whole-brain three-dimensional (3D) T1-weighted MPRAGE sequences; detailed MRI acquisition protocol is provided in Supplemental Table 1) from 37 pedMS patients at first attack and 21/37 patients at follow-up were compared to matched healthy controls from the National Institutes of Health (NIH) Paediatric MRI Data Repository. This repository was created by the NIH MRI Study of Normal Brain Development as a multisite, longitudinal study of healthy and normal developing children conducted by the Brain Development Cooperative Group (MRI scans acquired at 1.5 T).[9] Corresponding to our patients' MRI acquisition after a 2-year time interval, repeated MRI scans in the NIH study were performed also in intervals of 2 years.

MRI scans of our patients were acquired at 1.5 T (five patients at 3 T; exclusion of five patients scanned at a 3 T MRI scanner showed no difference in results; Supplemental Figure 4). In addition, we included MRI scans from 37 age- and sex-matched controls with other neurological disorders (OND; e.g. migraine, tension-type headache) and normal cerebral MRI study all recruited at one of the major study sites (Children' Hospital Datteln, Witten/Herdecke University; all MRI scans acquired at 1.5 T).

MRI pre-processing was performed using the FMRIB Software Library FSL (https://fsl.fmrib.ox.ac.uk/fsl) and included the following steps: FLAIR and T1 images

Table 1. Demographic and clinical parameters of the cohort of 37 children with MS.

	Patients ($n=37$)	
	n	%
Median age at onset (range, years)	15.0 (10–17)	
Female patients	18	48.6
OCBs		
OCBs positive	31	83.8
OCBs negative	5	13.5
Not tested	1	2.7
Median CSF cell count (range, per µL)	7.5 (0–52)	
Mean time between MRIs (months ± SD)	24.76 ± 6.8	
EDSS score (median, range)	0 (0–2)	
Relapses in first 2 years (median, range)	2 (1–5)	
Disease-modifying therapy in the first 2 years		
Interferon beta (2 + Nata; 1 + Glati)	10	27.0
Natalizumab (2 + INF)	5	13.5
Glatiramer acetate (1 + INF)	1	2.7
MRI lesion load (T2w/FLAIR) at first MRI		
Total lesion count (median, range)	4 (1–10)	
Supratentorial lesion count	4 (0–9)	
Infratentorial lesion count	0 (0–7)	
Lesion score 1–3 (1–5/6–10/ >10)	2 (1–3)	

SD: standard deviation; CSF: cerebrospinal fluid; EDSS: Expanded Disability Status Scale; OCBs: oligoclonal bands; Nata: natalizumab; Glati: glatiramer acetate; INF: interferon beta; MRI: magnetic resonance imaging.

were linearly co-registered, T1 images were brain extracted and a WM mask was generated from brain-extracted T1 images. FLAIR images were then used to run automatic lesion segmentation with the lesion prediction algorithm as implemented in the LST toolbox version 2.0.15 for SPM (www.statistical-modelling.de/lst.html).[10] Automatic lesion segmentation was visually assessed by two independent investigators (G.C. and F.B.) and manually corrected, if necessary. Generated lesion and WM masks and original T1 images were inputted to the FSL lesion filling tool generating images for further volumetric analyses.[11] Brain volume of lesion-filled T1 images, normalized for subject head size (computed scaling factor), was then estimated using FSL SIENAX.[12,13] SIENAX uses tissue-type segmentation estimating normalized whole brain volume (WBV), grey matter volume (GMV), white matter volume (WMV), peripheral grey matter volume (pGMV), and ventricular CSF (vCSF; unnormalized values and scaling factors shown in Supplemental Table 2).

Mean patient volumes at first presentation and at follow-up were compared 1:5 to age- and sex-matched healthy controls (patients vs controls; age: 14.62 ± 1.72 years vs 14.74 ± 1.79 years, $p=0.723$; female: 48.6% vs 56.8%, $p=0.365$) and at follow-up (age, 16.91 ± 1.22 years vs 16.90 ± 1.09 years, $p=0.928$; female: 42.9% vs 54.3%; $p=0.342$). Supplemental Figure 1 shows MRI measurements (WBV) on a subset of patients to illustrate study design with first MRI scan at initial presentation and follow-up MRI scan after 2 years with corresponding time intervals in matched healthy controls. The *z*-scores were calculated for each patient MRI volume for further longitudinal and correlation analyses. To this end, an individually matched normative control group with same sex and age (±3 months) was identified for each patient MRI (baseline and follow-up). Patient *z*-scores were then computed with the following formula: $Z = (v - \mu) / \sigma$, where Z is the patient brain volume *z*-score, v is the patient brain volume, μ is the mean brain volume of the corresponding individual normative control group, and σ is the standard deviation (SD) of the control group.

To verify automatic lesion segmentation, T2 lesion load was additionally evaluated based on whole brain T2-weighted and/or FLAIR sequences by two independent investigators (K.N. and B.C.) with mean values used for further analyses. Infratentorial, supratentorial, and total lesion count as well as a total lesion load score (scale 1–3; score 1 = 1–5 lesions; score 2 = 6–10 lesions; score 3 ⩾ 10 lesions) were calculated. Intraclass correlation (ICC) analysis revealed a robust interrater correlation: supratentorial lesion count

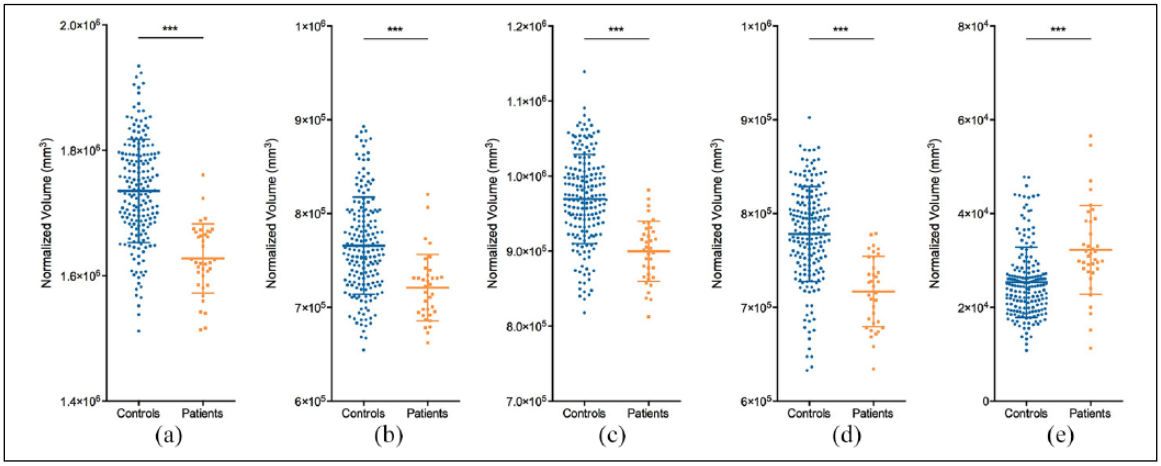

Figure 1. Brain atrophy at first clinical presentation. Normalized brain volumes (mm^3) at first clinical presentation. All brain volumes are significantly smaller in MS patients ($n=37$) at disease onset compared to matched (1:5) healthy controls ($n=185$): (a) whole brain volume, (b) white matter volume, (c) grey matter volume, (d) peripheral grey matter volume, and (e) ventricular CSF volume.

ICC = 0.836, Cronbach's alpha = 0.909; infratentorial lesion count ICC = 0.914, Cronbach's alpha = 0.954 and total lesion count ICC = 0.889, Cronbach's alpha = 0.94.

Statistical analysis

Shapiro–Wilk test was used to assess distribution of data revealing normal distribution of brain volumes and brain volume *z*-scores in both groups. Volumetric group differences were analysed using student's *t*-test. Patient *z*-scores were compared against expected healthy control volume (zero) using Wilcoxon test, and *z*-score change from baseline to follow-up was analysed using paired *t*-test. Correlation analyses were performed using Spearman's rank correlation rho. All statistical tests were two-sided and p values <0.05 were considered significant. Correction for multiple comparison was not applied due to the exploratory study design. IBM SPSS Statistics for Windows (Version 22®; IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Reduced brain volume at first presentation (cross-sectional analysis)

PedMS patients had significantly smaller brain volume at first presentation compared to matched healthy controls with significantly reduced WBV (mean ± standard error of mean (SEM); $1627.5\,cm^3 \pm 9.1$ vs 1735.3 ± 6.1; $p<0.001$), GMV (894.3 ± 8.5 vs 969.5 ± 4.4; $p<0.001$), pGMV (708.9 ± 8.2 vs 778.2 ± 3.7; $p<0.001$), and WMV (733.3 ± 10.7 vs 765.8 ± 3.8; $p<0.001$; Figure 1(a)–(d)). vCSF at baseline was significantly increased compared to healthy controls (32.2 ± 1.6 vs 25.8 ± 0.6; $p<0.001$; Figure 1(e)). Total intracranial volume (scaling factor) and unnormalized brain volumes were also significantly reduced in patients compared to matched controls (Supplemental Table 2). An additional analysis confirmed brain volume loss in patients at first presentation compared to age- and sex-matched controls (1:1) with OND and normal cerebral MRI scans from one of the major study sites (Supplemental Table 3).

Brain volume loss at follow-up (cross-sectional analysis)

Analyses of follow-up scans revealed persistent reduced brain volume compared to matched healthy controls with reduced WBV ($1595.1\,cm^3 \pm 12.7$ vs 1711.8 ± 7.3; $p<0.001$), GMV (873.1 ± 11.3 vs 939.1 ± 5.0; $p<0.001$), pGMV (699.8 ± 9.3 vs 753.2 ± 4.3; $p<0.001$), and WMV (722.1 ± 13.3 vs 772.7 ± 5.4; $p<0.001$; Figure 2(a)–(d)), while vCSF was significantly increased (37.3 ± 2.7 vs 26.7 ± 1.0; $p=0.001$; Figure 2(e)).

Accelerated brain volume loss after first presentation (longitudinal analysis)

Next, all patient brain volumes were individually *z*-transformed based on age- and sex-matched normative control groups. The patients' mean *z*-scores of all brain structures were significantly smaller than zero at baseline (all $p<0.01$) and at follow-up (all $p<0.001$). Accordingly, patients' vCSF volume *z*-scores were significantly higher than zero at baseline and follow-up (all $p<0.001$). Over the course of 2 years, patient's *z*-scores

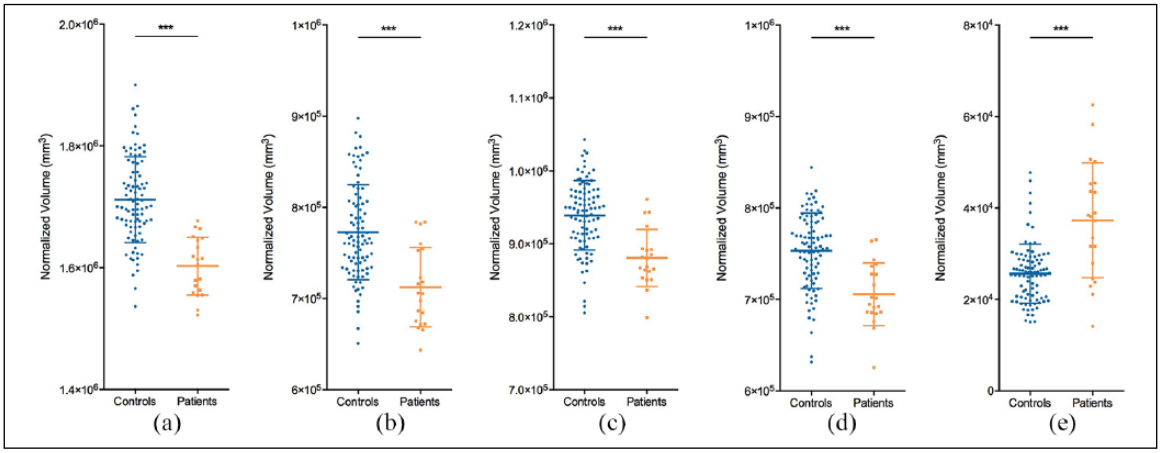

Figure 2. Brain atrophy at 2-year follow-up. Normalized brain volumes (mm^3) at 2-year follow-up. All brain volumes are significantly smaller in MS patients ($n=21$) after 2 years compared to matched (1:5) healthy controls ($n=92$): (a) whole brain volume, (b) white matter volume, (c) grey matter volume, (d) peripheral grey matter volume, and (e) ventricular CSF volume.

showed a significant reduction for WBV (baseline vs follow-up; mean ± SEM; −1.30 ± 0.23 vs −1.71 ± 0.22; $p=0.033$) and for WMV (−0.53 ± 0.36 vs −1.07 ± 0.28; $p=0.015$), but not for GMV (−1.49 ± 0.32 vs −1.51 ± 0.32; $p=0.937$) and pGMV (−1.58 ± 0.34 vs −1.48 ± 0.34; $p=0.604$), suggesting accelerated brain volume loss in patients compared to healthy controls driven by accelerated WM loss (Figure 3(a)–(d)). Correspondingly, patients' vCSF volume increased significantly between first presentation and follow-up (0.80 ± 0.33 vs 1.62 ± 0.41; $p<0.001$; Figure 3(e)).

Brain volume loss correlates with disease severity

Total median MRI lesion count on baseline MRI was 4 (range: 1–10) with a median of 4 (0–9) supratentorial lesions and 0 (0–7) infratentorial lesions. The median lesion score was 2 (range: 1–3). The number of infratentorial lesions on T2w/FLAIR images at baseline showed a significant correlation with WBV and vCSF volume *z*-scores, both at first presentation and at follow-up (WBV Spearman's rho = –0.336 ($p=0.045$) and −0.325 ($p=0.008$); vCSF rho = 0.320 ($p=0.034$) and 0.306 ($p=0.011$)), suggesting a correlation between brain volume loss and increased disease activity (Figure 4(a) and (b)). In addition, WMV *z*-scores at follow-up were significantly smaller in patients with higher lesions scores (score 3 vs 2: −1.62 vs −0.21; $p=0.016$, but not score 3 vs 1 (–1.62 vs −0.81; $p=0.205$)). The number of relapses within the first 2 years of the disease correlated significantly with vCSF volume *z*-score at follow-up (rho = 0.499; $p=0.025$), suggesting a correlation of relapse rate with brain atrophy (Figure 4(c)). Furthermore, patients with an EDSS of 1 after 2-year follow-up showed significantly smaller WBV *z*-scores compared to patients with an EDSS score of 0 (–2.38 vs −1.37; $p=0.022$), indicating a possible association between clinical disease activity and brain atrophy.

At follow-up, 13 patients (61.9%) received DMTs, including interferon beta, natalizumab, and glatiramer acetate. Patients with DMTs showed no significant benefit regarding brain volume at follow-up compared to non-treated patients (DMTs vs no treatment; −1.97 vs −1.39, $p=0.170$). Indeed, patients treated with natalizumab showed larger vCSF volume *z*-scores at baseline as well as at follow-up (1.78 vs 0.63; $p=0.058$ and 3.40 vs 1.06; $p=0.010$), suggesting a potential treatment bias. As expected, patients treated with natalizumab showed signs of increased disease activity as reflected in a significantly increased lesion load at baseline (infratentorial and total lesions; 3.4 vs 1.2, $p=0.19$ and 10.0 vs 4.2, $p=0.049$), and a higher number of relapses over the period of 2 years (3.4 vs 2.1, $p=0.026$).

Discussion

Our analyses show that pedMS patients have significant brain volume loss affecting WBV and GMV and WMV in association with increased ventricular volume already at first clinical presentation. Furthermore, we show that patients continue to have further brain volume loss over the following 2 years compared to controls irrespective of treatment with DMTs. Our study further indicates that accelerated brain volume loss correlates with higher disease activity as suggested by the number of relapses, T2/FLAIR total lesions load and higher EDSS scores after 2 years.

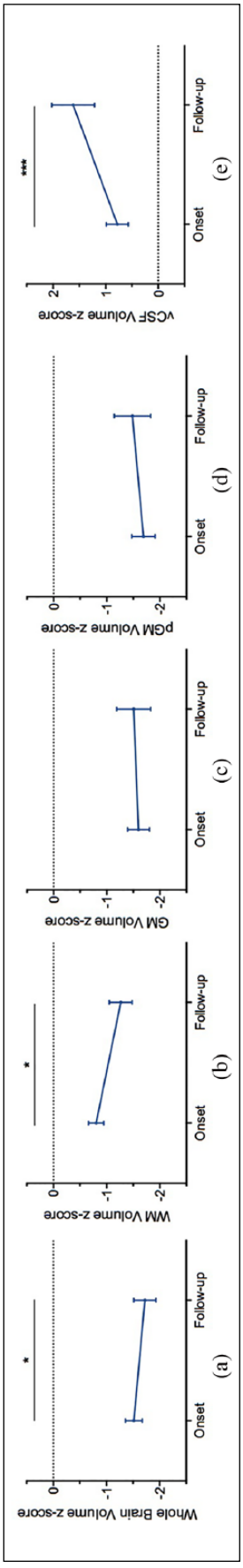

Figure 3. Failure of brain growth over 2-year follow-up. Mean brain volume *z*-scores at onset (first clinical presentation) and at follow-up after 2 years (mean ± SEM). Whole brain volume and white matter volume *z*-scores show significant reduction over 2 years, indicating accelerated brain volume loss in MS patients compared to healthy controls. Accordingly, patients show a significant increase in ventricular CSF volume (vCSF) *z*-scores over 2 years: (a) whole brain volume, (b) white matter volume, (c) grey matter volume, (d) peripheral grey matter volume, and (e) ventricular CSF volume.

In adult MS patients, brain volume loss as assessed with MRI has become a well-established marker of disease-related atrophy and is increasingly used as an endpoint in clinical trials.[14–17] MR imaging in children with MS has so far mainly been used to support or confirm the diagnosis after a clinical attack and to monitor subclinical disease activity. Recently, a cross-sectional quantitative MRI analysis in children with MS (mean disease duration 3.1 years) clearly demonstrated that also pedMS patients have reduced brain volume.[6] Moreover, a second study showed that pedMS children have reduced brain volume early in their disease (mean disease duration before first MRI 1.2 years) and, importantly, longitudinally fail to achieve their expected brain growth trajectory.[7]

Here, we complement these important studies by demonstrating that pedMS patients have reduced brain volume compared to healthy controls already at first clinical presentation and, importantly, before application of intravenous corticosteroids. This is in line with MRI studies in adult MS patients that repeatedly documented brain atrophy even before clinical presentation.[18,19] Our study suggests that in pedMS patients alike, brain volume loss, and therefore probably disease activity, most likely begins already prior to first clinical presentation. On first MRI, volumes of both grey and white matter were reduced compared to age- and sex-matched healthy children, with GM being relatively more affected compared to WM as indicated by lower GM versus WM volume *z*-scores. Similarly, in adult MS patients, cross-sectional studies showed early atrophy of both GM and WM compared to healthy controls.[20–22] The structured follow-up after 2 years in patients and controls allowed for an accurate evaluation of brain volume development over this time period in our study. Following reduced GM and WM volume at first presentation, we observed that pedMS patients experience further and accelerated brain volume loss in comparison to healthy controls over time. Importantly, our data suggest that this additional brain volume loss is primarily driven by accelerated WM loss as significant volume reductions were only found for whole brain and WM, but not GM volume. This is in contrast to previous findings in adult patients where brain volume loss seems to be mainly driven by loss of GM volume.[21,23] Similar to our findings of predominant WM loss over 2 years in pedMS patients, children with monophasic acquired demyelinating syndrome (ADS; acute disseminated encephalomyelitis (ADEM) and clinically isolated syndrome (CIS)) were shown to have reduced age-expected brain growth driven by reduced WM growth.[24] Interestingly, a recent study demonstrated marked loss of WM

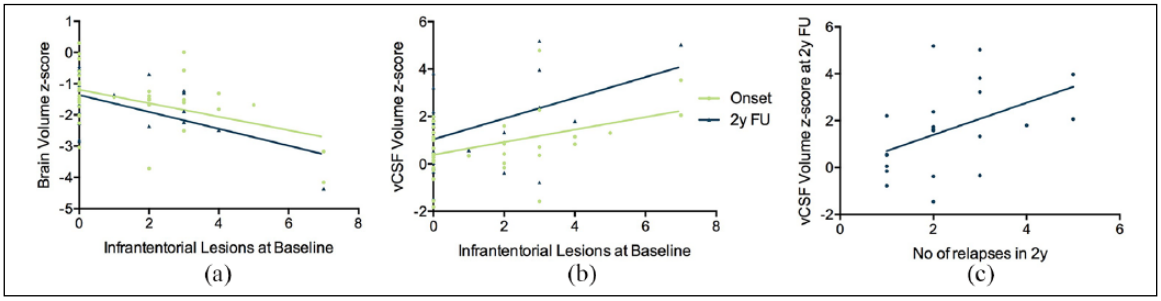

Figure 4. Brain atrophy correlates with infratentorial lesions and number of relapses: (a) infratentorial lesion count shows an inverse correlation with brain volume and (b) a positive correlation with ventricular CSF (vCSF) *z*-scores at onset and at follow-up suggesting an association of infratentorial lesion accumulation and brain atrophy. (c) The number of relapses during first 2 years of disease course correlates with ventricular CSF (vCSF) *z*-scores at follow-up, suggesting a correlation between number of relapses and brain volume loss.

integrity in pedMS patients due to potential axonal injury, as shown by diffusion tensor imaging changes across time.[25]

In order to exclude scanner-related confounding effects, we additionally compared patient MRI scans to scans of patients with OND and normal cerebral MRIs selected from one of the main study sites. This comparison also confirmed the reduced brain volume in patients with pedMS. However, it is important to note that, in contrast to the healthy controls of the NIH cohort, these subjects represent a cohort with different neurological disorders (e.g. chronic headache, etc.) prompting cerebral MRI imaging. Nevertheless, the significantly reduced brain volume of pedMS patients compared to these controls with normal MRI scans further substantiate that pedMS patients experience brain volume loss early in their disease.

We could further show that brain volume loss in pedMS patients correlates with disease activity, that is, lesion load, number of relapses and increased EDSS score. The total number of lesions as reflected by an overall higher lesion score correlated with reduced WM volume at follow-up. Moreover, a higher infratentorial lesion load at baseline correlated with reduced brain volume at baseline and follow-up. Indeed, infratentorial lesions are more frequent and of larger volume in pedMS patients compared to adult MS patients, which is in line with more frequent brainstem symptoms in pedMS patients.[26,27] Importantly, infratentorial lesions are also associated with increased long-term disability and poor prognosis.[28–30] In adult MS patients, the extent of lesion load especially in the first years was shown to influence subsequent long-term brain atrophy.[31] We here show that this might be true also in pedMS patients, warranting early diagnosis and sufficient therapy.

Similarly, patients with a higher number of relapses showed an increased vCSF volume at follow-up, further substantiating the relationship between clinical disease activity and brain volume loss. In adult MS patients, brain volume loss was shown to highly correlate with the number of relapses based on cumulated data from more than 3.500 patients.[32] To our knowledge, our study is the first to show this correlation of brain volume loss and the number of relapses in pedMS patients. Furthermore, we show that in pedMS patients, more severe brain atrophy is associated with more clinical symptoms as indicated by higher EDSS scores after 2 years, providing a link between MRI volumetric measures and disease progress. As in most pedMS patients, the patients' EDSS scores in our study were low so that correlations with EDSS score have to be interpreted with caution. Nevertheless, as shown above, correlations of brain volume loss with disease activity are also linked to increased lesion load and higher number of relapses, which are considered robust indicators of disease activity.

Longitudinal brain volume loss has become an important outcome parameter in adult MS treatment trials. Although not the main focus of the study design, we evaluated in an exploratory approach if the application of DMT at any time point in the first 2 years had an influence on brain volume loss in our cohort. We observed no difference in brain volume at follow-up between patients with and without DMTs. Five children were treated primarily or escalated to natalizumab. These patients showed more brain volume loss compared to patients treated with other DMTs or no treatment–most likely because they belong to a subgroup of children with high disease activity, as indicated by a higher lesion load at baseline and a higher relapse rate. The increased brain volume loss

in these patients could therefore either be attributed to higher disease activity and thus increased atrophy, or alternatively, to pseudoatrophy following highly effective therapy. However, these analyses should be interpreted with caution due to the relatively small sample number of children receiving DMTs and the inability to take the length and type of treatment into account. Thus, this question requires further evaluation in future prospective studies.

A limitation of this study is its multicentre design with different MRI scanners at participating sites. However, the applied analysis software packages were shown to be robust to scanner differences and are also routinely used in large multicentre adult MS trials. Furthermore, to rule out scanner-related biases, an additional comparison of brain volumes in pedMS patients to a matched patient group with OND and normal cerebral MRI scans from one of the study sites as well as an additional subgroup analysis of patients scanned at 1.5 T only both confirmed the previous results of reduced brain volume in pedMS patients. Indeed, the multicentre design also has relevant advantages, since it provides a more representative patient sample, reduces the risk for bias and increases the robustness and generalizability of our results. Nevertheless, future studies should apply standardized protocols to exclude potential scanner biases. Furthermore, the use of the same control cohort as in previous studies on pedMS brain volume allows for an optimal comparison of detected effects. Another limitation is the small number of patients with MRI at follow-up. This is due to the restriction to patients with available high-resolution 3D MRI data (MPRAGE) to reliably detect volume differences, that is, reducing sample size to increase data quality. Brain volume measurement can be confounded by pseudoatrophy, that is, transient drug-induced MRI brain volume reduction, for example, after steroid treatment.[33] While we cannot entirely exclude this phenomenon in the follow-up MRI analysis, all MRI scans at first presentation were performed before administration of corticosteroids such as intravenous methylprednisolone, thus excluding potential drug impacts on MRI brain volume.

We show in a European cohort of pedMS patients that brain volume loss can be detected already at first clinical presentation and that brain volume loss continues over the following 2 years despite the application of DMTs. High lesion load at baseline and an increased number of relapses within the first 2 years are associated with more severe brain volume loss. Brain atrophy already at first clinical presentation and continuing brain volume loss over time indicate potential disease activity prior to first presentation as well as early neurodegeneration. Recent sample size estimations suggest that multicentre collaborations are needed to adequately power clinical trials in pedMS.[34] Our study adds to increasing evidence that such collaborative studies at multiple sites with shared MRI protocols and different scanners are feasible and that MRI-derived brain volume change might become a valuable outcome measure in future prospective trials in pedMS patients.[35,36]

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Carsten Finke and Kevin Rostásy equally contributed to this article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: Frederik Bartels and Carsten Finke report no conflict of interest. Rostásy served as a consultant for the PARADIGMS study, sponsored by Novartis, but received no payment and received honoraria from Merck.

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Supplemental material

Supplemental material for this article is available online.

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