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ORIGINAL ARTICLE

Early spinal cord pseudoatrophy in interferon-beta-treated multiple sclerosis

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Abstract

Background and purpose: Brain pseudoatrophy has been shown to play a pivotal role in the interpretation of brain atrophy measures during the first year of disease-modifying therapy in multiple sclerosis. Whether pseudoatrophy also affects the spinal cord remains unclear. The aim of this study was to analyze the extent of pseudoatrophy in the upper spinal cord during the first 2 years after therapy initiation and compare this to the brain.

Methods: A total of 129 patients from a prospective longitudinal multicentric national cohort study for whom magnetic resonance imaging scans at baseline, 12 months, and 24 months were available were selected for brain and spinal cord volume quantification. Annual percentage brain volume and cord area change were calculated using SIENA (Structural Image Evaluation of Normalized Atrophy) and NeuroQLab, respectively. Linear mixed model analyses were performed to compare patients on interferon-beta therapy ($n = 84$) and untreated patients ($n = 45$).

Results: Patients treated with interferon-beta demonstrated accelerated annual percentage brain volume and cervical cord area change in the first year after treatment initiation,

whereas atrophy rates stabilized to a similar and not significantly different level compared to untreated patients during the second year.

Conclusions: These results suggest that pseudoatrophy occurs not only in the brain, but also in the spinal cord during the first year of interferon-beta treatment.

KEYWORDS
brain, MRI, multiple sclerosis, pseudoatrophy, spinal cord

INTRODUCTION

Quantification of changes in brain volume by use of structural magnetic resonance imaging (MRI) is of crucial importance for the assessment of neurodegeneration in multiple sclerosis (MS). Associations between clinical disability and brain volume measures made brain atrophy the most prominent MRI biomarker in MS [1–3]. The quantification of brain volume changes is very important for clinical trials, as it can be used to demonstrate treatment efficacy. The refinement of interpreting such results is therefore a critical factor for the assessment of treatment effects. In addition to brain atrophy, spinal cord (SC) atrophy has gained increasing interest in recent years as a parameter associated with clinical disability [4, 5]. Although applications of SC volumetry for treatment monitoring remain limited, several studies highlighted its relevance as a marker for clinical disability and disease progression [6, 7], with annual atrophy rates exceeding those observed for brain atrophy [8].

However, several confounders must be considered when interpreting the temporal dynamics of volume changes over time. Brain pseudoatrophy (PA), well known to affect MS patients [9, 10], describes a marked decrease in brain volume within the first year after initiation of interferon or natalizumab [11, 12]. This may be due to a resultant reduction in diffuse parenchymal edema, which can be caused by inflammatory MS lesions and by subtle subclinical inflammatory processes [13]. PA may therefore limit the sensitivity of detecting the possible early neuroprotective effects of some immunotherapies. Accordingly, several studies have reported accelerated brain atrophy rates within the first year of treatment, which could be caused or overshadowed by remission of inflammatory lesions or accompanying edema because of therapy.

Although therapy-induced PA in the brain has been extensively studied, only a few studies have investigated therapy-induced effects on SC [14–17]. In this multicentric, longitudinal study, we aimed to quantify both SC and brain atrophy within the first 2 years after initiation of disease-modifying therapy (DMT) in patients with newly diagnosed MS or clinically isolated syndrome (CIS). We investigated differences between patients receiving interferon-beta therapy who are the most likely to demonstrate PA and patients not on treatment and hypothesized that, similar to the brain, therapy-related PA may be detectable in the upper cervical cord. Our study therefore had two objectives: first, to confirm PA effects on the brain in patients receiving early interferon-beta therapy, and second, to investigate whether PA could be detected in the SC in the same population. This information may serve as a cornerstone for the future interpretation of SC atrophy in MS.

METHODS

Patients

We included patients from the prospective longitudinal multicenter German National MS Cohort Study of the German Competence Network Multiple Sclerosis (KKNMS), for which patients have been recruited since 2010. According to the study design, the enrolled patients were DMT-naïve prior to inclusion. All patients fulfilled the diagnosis of CIS within the 6 months prior to inclusion, or early definite relapsing–remitting MS (RRMS) based on the McDonald 2010 criteria [18]. The decision on administering medication was jointly taken by the respective centers and the patients, depending on their individual demands and in accordance with the current guidelines for treatment of MS. Study details have been described elsewhere [19]. The patient inclusion procedure for our study is schematically described in Figure 1.

Magnetic resonance imaging

Imaging was performed using a standardized MRI brain imaging protocol at 3 T. The MRI protocol was harmonized across centers regarding image resolution and contrast and included high-resolution, isotropic three-dimensional (3D) T1-weighted (T1w) and 3D fluid-attenuated inversion recovery (FLAIR) sequences with a field of view covering the brain and the upper cervical cord (Table S1). All sites used the vendor-specific 3D distortion correction procedures to correct for nonlinear gradient distortion effects [20].

Measurements of the mean upper cervical cord area (MUCCA) were performed based on the brain 3D T1w datasets using the semiautomatic software NeuroQLab (v4.01, release date 6 August 2016, Fraunhofer MEVIS) as previously described [5]. This method was recently shown to be a reliable and sensitive measure for quantification of upper SC cross-sectional area from brain images [20]. MUCCA (mm^2) was assessed in a predefined cord section of 40 mm length between the C1 and C3 vertebrae, starting at the top of C1. The mean cord area was calculated by dividing the segmented cord volume by the section length (Figure 2).

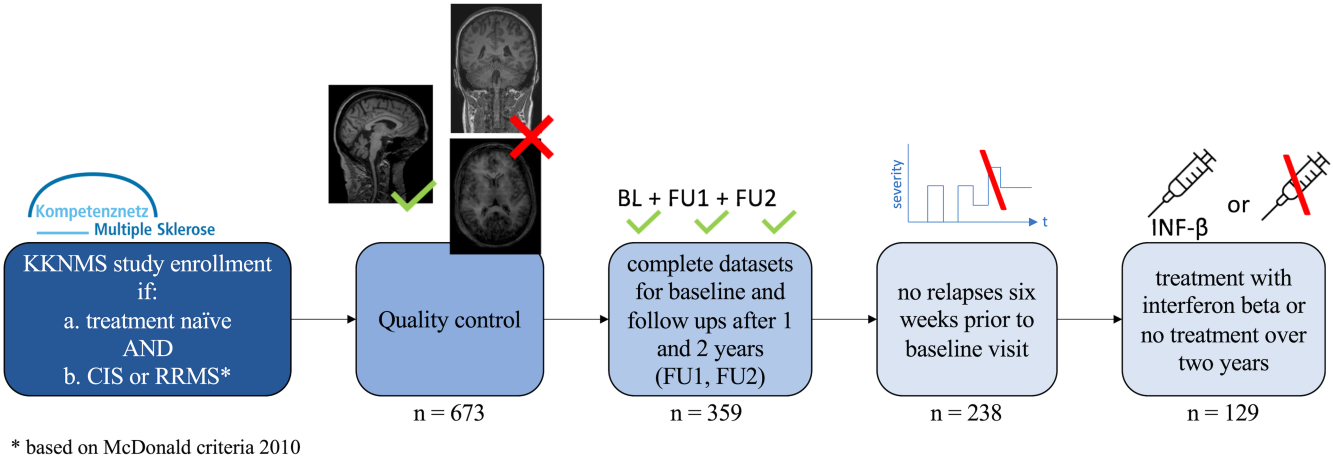

FIGURE 1 Flowchart of the patient inclusion procedure. The requirements for inclusion covered sufficient image quality, two complete magnetic resonance imaging acquisitions within the first 2 years, no relapse within 6 weeks before baseline visit, and continuous interferon (INF) therapy or no medication during the following 2 years. BL, baseline; CIS, clinically isolated syndrome; FU1, follow-up after 1 year; FU2, follow-up after 2 years; KKNMS, German Competence Network Multiple Sclerosis; RRMS, relapsing–remitting multiple sclerosis

Annual percentage cord area change (aPCAC) was calculated between baseline (BL) and follow-up after 1 year (FU1) as well as between FU1 and follow-up after 2 years by

$$\text{aPCAC} = \frac{\text{MUCCA}_{t2} - \text{MUCCA}_{t1}}{\text{MUCCA}_{t1}} \times \frac{1}{(t2 - t1)}$$

where $t1$ and $t2$ represent time of the first and the second MRI scans, resulting in negative aPCAC rates if the cord area decreases.

To estimate the annual percentage brain volume change (aPBVC) for the first and the second years, registration-based Structural Image Evaluation of Normalized Atrophy (SIENA) software, part of the FMRIB Software Library (FSL) [21], was used. Before using SIENA, we cropped the 3D T1w datasets to exclude parts containing the cervical cord using FSL's robustfov. Instead of the default brain extraction tool (BET) options, a fractional intensity threshold of 0.3 and the option for bias field correction and neck cleanup were used. In addition, 3D T1w datasets were corrected for brain hypointense lesions by lesion-filling based on the corresponding FLAIR lesion maps with 3D T1w series as reference datasets using the lesion prediction algorithm [22] included in the lesion segmentation toolbox (lesion prediction algorithm of LST toolbox version 2.0.15; www.statistical-modelling.de/lst.html). The resulting volume changes were annualized to account for individual differences in the observation period.

To overcome methodological differences between brain and SC volume assessments, we further calculated atrophy rates based on cross-sectionally quantified brain volumes using FSL-SIENAX. For that, total brain, gray matter (GM) and white matter (WM) volumes normalized for head size by use of the estimated scaling factor were used, and the same calculation as for aPCAC was applied.

Prior to analyses, all MRI scans were visually inspected. We excluded MRI scans from the NeuroQLab analysis if insufficient image quality due to movement or swallowing artifacts or severe signal to noise reductions in image parts covering the cervical cord were detected. Brain data were excluded if a 3D FLAIR sequence was not available, if severe brain abnormalities, such as extreme deformations, were observed, and if the quality control of the SIENA pipeline indicated incorrect segmentation results.

Information on gadolinium-enhancing (Gd+) lesions in the brain were extracted from the study database. The occurrence of Gd+ lesions or hypointense lesions in T1w contrast in the upper cervical cord (C1–C3 vertebrae) was visually assessed based on pre- and post-Gd sagittal 3D T1w scans.

Statistical analysis

To analyze differences in atrophy rates between patients with and without interferon-beta therapy, we used linear mixed models with age and gender as fixed effects and center as a random effect. To account for possible cofounding effects of acute inflammatory lesions, we further included the presence of Gd+ brain lesions and SC lesions (hypointense on 3D T1w images) as fixed effects. All analyses and graphical representation were performed in R [23].

Standard protocol approvals, registrations, and patient consent

The study was approved by the local ethics committee of Ruhr University Bochum (approval No. 3714–10), and all patients provided written informed consent prior to study participation.

RESULTS

From the total number of patients enrolled in the KKNMS cohort, the presented study included 129 patients (77 CIS and 52 RRMS) from eight centers after quality control and exclusion of

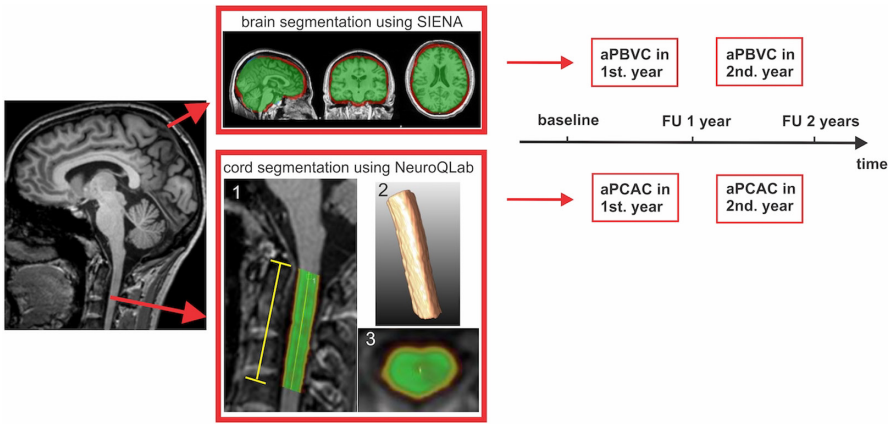

FIGURE 2 Schematic representation of quantification of annual percentage brain volume change (aPBVC) and annual percentage cord area change (aPCAC) using Structural Image Evaluation of Normalized Atrophy (SIENA) and NeuroQLab, respectively. Measures were assessed for the first year between baseline and the first follow-up (FU 1 year) magnetic resonance imaging acquisition, and for the second follow-up (FU 2 years). For spinal cord segmentation, a predefined cord section of 40-mm length between the C1 and C3 vertebrae was assessed (1), which was used to segment the cord volume (2), and the mean cord area (3) was calculated by dividing the segmented cord volume by the section length

insufficient data. The participants were divided into patients with interferon beta-1b or beta-1a treatment starting 5 days (median; interquartile range = 5–24.5 days) after the BL MRI examination (n = 84) and patients without any therapy during the follow-up interval (n = 45; Figure 1).

BL demographic data and clinical features of the patients included in the final analyses of this study are detailed in Table 1. No significant differences were observed for the described demographic group characteristics at BL (Welch two-sample t-test; Table 1). Disease duration was set as the time of symptom onset, which was slightly shorter for CIS patients (mean = 0.60, SD = 0.48) than for MS patients (mean = 0.84, SD = 0.60). Because the collection of information on oligoclonal bands (OCBs) was not mandatory within the KKNMS study procedure, we were able to collect this for two thirds of our study sample. Within this subgroup, 42 CIS patients and 26 MS patients showed OCBs.

Only one patient had a contrast-enhanced lesion in SC at BL and five patients at one of the follow-up scans, so that this variable was not considered for further analyses.

Brain atrophy

Patients on interferon-beta therapy demonstrated accelerated aPBVC during the first year compared to untreated patients. There were no differences between the groups with or without interferon-beta treatment during the second year (Table 2, Figure 3).

Similarly, the additional quantification of indirect brain atrophy rates based on cross-sectional technique yielded significantly accelerated atrophy rates in patients treated with interferon-beta compared to untreated patients in the first year, but not in the second year. However, we excluded eight patients because of rates higher than ±5%, which was caused by the more improper methodology, compared to the registration-based approach. WM atrophy rates showed the same behavior as total brain atrophy rates, whereas for GM atrophy only a trend toward accelerated rates in the first year was observed. The results are summarized in the supplement.

SC atrophy

Comparison of patients on interferon-beta and untreated patients yielded significantly accelerated aPCAC from BL to FU1 for the interferon-beta group. Similar to brain atrophy, no differences between the groups in SC atrophy were observed during the second year. Overall, the variability of aPCAC was considerably higher than the variability of the brain atrophy rates (Table 2, Figure 3).

Influence of Gd+ and SC lesions

As obtained from the summary statistics about the fixed effects in the mixed models, Gd+ did not have a significant influence on brain atrophy (first year: $p = 0.87$, second year: $p = 0.34$), nor did the presence of hypointense T1w SC lesions have a significant effect on SC atrophy (first year: $p = 0.44$, second year: $p = 0.13$).

DISCUSSION

In this longitudinal study, we evaluated the effect of interferon-beta treatment on brain and SC atrophy in patients with newly diagnosed MS or CIS within the first 2 years after therapy initiation. This study is based on a circumscribed but well-characterized sample of patients, as it constituted real-world multicentric data from a large national cohort study. The analyses were conducted on a homogenous sample with constant or without treatment for 2 years. We

TABLE 1 Demographic data and clinical features of included patients at baseline

Characteristic	Overall, $N = 129$[a]	Interferon, $n = 84$[a]	No therapy, $n = 45$[a]	p[b]
Sex				
Female	86 (67%)	54 (64%)	32 (71%)	0.6
Male	43 (33%)	30 (36%)	13 (29%)	
Age, years	34 (10)	33 (10)	37 (9)	0.015
Expanded Disability Status Scale	1.0 (0.0–3.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	>0.9
Sensory score	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.7
Pyramidal score	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	>0.9
Disease duration, years	0.70 (0.54)	0.68 (0.56)	0.73 (0.53)	0.6
Classification per McDonald 2010				
CIS	77 (60%)	51 (61%)	26 (58%)	0.9
RRMS	52 (40%)	33 (39%)	19 (42%)	
Treatment				
Avonex		28 (33%)		
Betaferon		12 (14%)		
Rebif 22 µg		15 (18%)		
Rebif 44 µg		29 (35%)		
Patients with Gd+ lesions	26 (20%)	17 (20%)	9 (20%)	>0.9
Not evaluated	2	2	0	
Patients with hypointense T1 upper cervical cord lesions	70 (55%)	47 (57%)	23 (51%)	0.6
Not evaluated	1	1	0	
Number of CIS/MS	43/27			0.7
Brain T2 lesion volume, ml	2.68 (2.48)	2.84 (2.59)	2.37 (2.26)	0.3
Normalized MUCCA, mm^2	80 (9)	81 (9)	79 (9)	0.3
Normalized total brain volume, ml	1487 (89)	1488 (88)	1485 (94)	0.9

Note: Normalized total brain volume was quantified using SIENAX, part of the FMRIB Software Library.

Abbreviations: CIS, clinically isolated syndrome; Gd+, gadolinium-enhancing; MS, multiple sclerosis; MUCCA, mean upper cervical cord area; RRMS, relapsing–remitting multiple sclerosis.

[a]n (%), mean (SD), or median (range).

[b]Fisher exact test or Welch two-sample t-test.

confirmed the presence of immunotherapy-associated PA in the brain and were able to detect PA in the upper SC for the first time. A significantly accelerated atrophy rate was observed for both brain and SC in the first year comparing interferon-beta-treated patients and DMT-naïve patients, but not in the second year.

Our PBVC results confirmed other studies investigating MS patients treated with interferon-beta, in which mean rates of −0.6% or −0.8% were observed during the first year [24, 25]. Whereas for aPBVC a cutoff of −0.4% was shown to be clinically relevant to define pathological brain volume loss [26], no threshold for a pathological SC atrophy rate has yet been defined.

Similar to the brain, we found that absolute aPCAC was significantly higher for patients treated with interferon-beta (−1.17%) than for untreated patients (−0.15%) in the first year, but not in the second year (−0.23% vs. 0.18%). Compared to other studies, aPCAC was lower than the previously proposed pooled SC atrophy rate of −1.78% per year [8]. However, those studies included progressive forms of MS. In another study, mean cervical cord changes of −1.68% in early RRMS and −0.25% in CIS patients were observed, but in contrast to our method, not only the upper cord was analyzed [27].

Thus, we were able to provide evidence for a PA effect occurring in the upper SC. Previous studies found longitudinal reduction of SC volumes in RRMS, but no reduction compared to healthy controls [15], and hypothesized that increased SC volumes might reflect inflammation and associated edema, which might be resolved by anti-inflammatory therapies [28]. Our finding of a more pronounced SC atrophy rate in the first year after therapy initiation supports this hypothesis. Previously, associations between hydration and SC changes have been described in healthy subjects, which demonstrated that such fluctuations of water content in the tissue, as would also be expected for edema and inflammation, have a measurable effect on SC volume [29]. In principle, the therapy-driven regression of acute inflammatory Gd+ lesions in SC could also contribute to a pseudoatrophy effect. However, due to our strict exclusion criteria, we observed almost no Gd+ lesions in our patient groups, so this

TABLE 2 Results of linear mixed model analyses for aPBVC and aPCAC between patients treated with interferon and untreated patients within the first (BL to FU1) and second year (FU1 to FU2) after therapy initiation

Parameter	emmean (SE)	Estimated difference	95% CI	*p*
aPBVC				
BL to FU1	Interferon: −0.64 (0.13) No therapy: −0.29 (0.16)	−0.35	−0.63 to −0.06	0.018
FU1 to FU2	Interferon: −0.45 (0.14) No therapy: −0.53 (0.19)	0.088	−0.24 to 0.42	0.595
aPCAC				
BL to FU1	Interferon: −1.17 (0.37) No therapy: −0.15 (0.45)	−1.01	−1.81 to −0.21	0.013
FU1 to FU2	Interferon: −0.23 (0.40) No therapy: 0.18 (0.47)	−0.41	−1.26 to 0.44	0.34

Abbreviations: aPBVC, annual percentage brain volume change; aPCAC, annual percentage cord area change; BL, baseline; CI, confidence interval; emmean, estimated marginal mean; FU1, follow-up after 1 year; FU2, follow-up after 2 years.

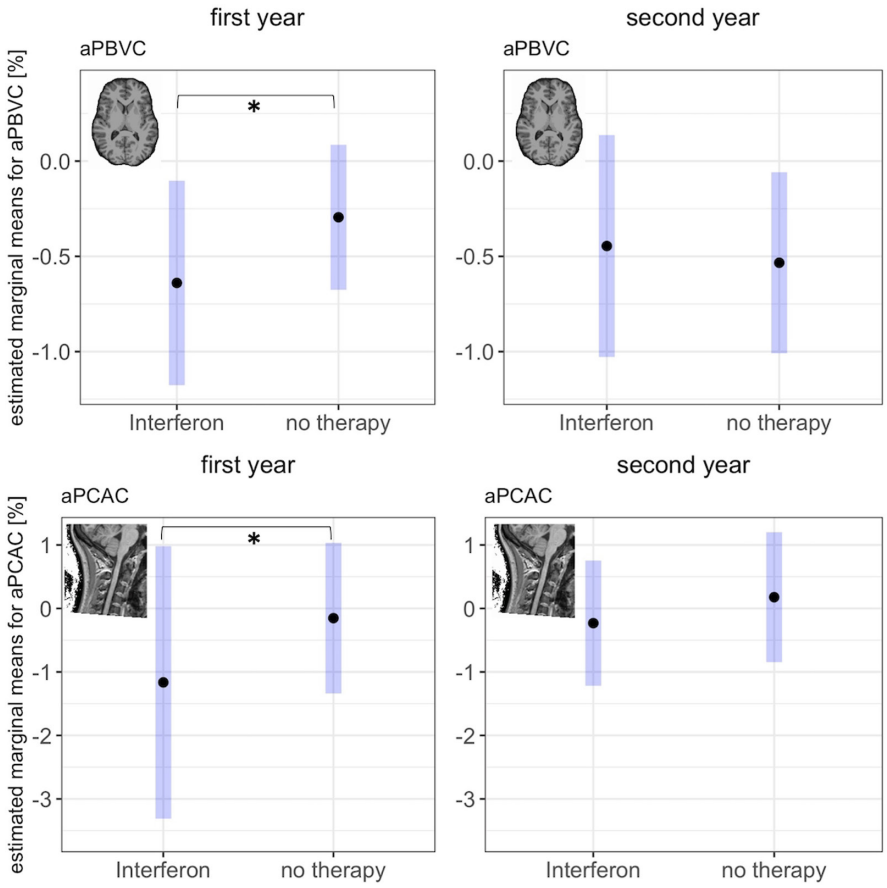

FIGURE 3 Estimated marginal means (black dots) from linear mixed model analyses for group comparisons of annual percentage brain volume change (aPBVC; first row) and annual percentage cord area change (aPCAC; second row) between interferon-beta-treated and untreated patients in the first (first column) and second year (second column). Bars represent 95% confidence intervals as obtained from mixed models. Significant group differences are marked with an asterisk

effect can be neglected here. The untreated patients examined in this study did not show a measurable reduction in SC volume within the first 2 years. Therefore, the observed spinal volume reduction in patients treated with interferon-beta might support the hypothesis of edema regression. In the untreated group, diffuse, ongoing atrophy might be masked by inflammation and edema, and treated patients may have had constant volumes over 2 years.

So far, few studies have investigated the effect of DMT on SC atrophy in MS. Leary et al. [14] compared a small group of progressive MS patients treated with interferon-beta with placebo and found no group differences regarding upper cervical atrophy rates over 2 years. Although the absence of SC changes was not discussed, they suggested that the anti-inflammatory effect of interferon-beta might contribute to brain atrophy. Similarly, Lin et al. [15] focused on the treatment effect of interferon-beta on SC atrophy in a small sample of both RRMS and progressive MS patients and found no differences between their placebo and treatment groups. Due to this lack of treatment effect on SC atrophy, they suggested that axonal loss might be caused by other mechanisms not directly related to inflammation. Recently, a large study on patients with primary

progressive MS assessed the potential treatment effects of laquinimod on upper SC atrophy between treated patients and a placebo group [30]. For both brain and SC atrophy measures, no treatment effect was detected. As these studies either were based on a small number of patients or included mainly progressive MS patients and different medications, comparability with our results is limited. Opposing effects regarding SC volume between progressive MS and RRMS patients have already been shown by Klein et al. [31]. They described a trend toward increased cervical cord volumes only in RRMS patients, interpreted as expansions caused by inflammation or edema, which would mask true atrophy [28].

Generally, SC atrophy seemed to be more pronounced than brain atrophy, suggesting a higher vulnerability to pathological changes in MS demonstrated by markedly degenerated SC [8]. However, SC atrophy exhibits high interindividual variability, which may be caused both by the small physical dimension and by confounding effects such as pulsation and motion artifacts during MRI acquisition. These effects not only contribute to interindividual variability of MUCCA but can also increase intraindividual variation between multiple MRI sessions. Additionally, MUCCA quantification based on brain MRI is susceptible to geometrical image distortions that may occur because the upper cervical cord is located off-center in the sagittal images, at the periphery of the field of view [20].

To assess the potential impact of methodological differences for brain and SC atrophy rate assessments in this study, we calculated the segmentation-based brain atrophy rates in addition to aPBVC from the registration-based approach. Although this method showed more outliers, which was most likely due to the more improper methodology compared to the longitudinal registration-based approach, we observed the same tendency of accelerated atrophy rates for interferon-beta-treated patients in the first year. This emphasized our results, as this constituted a more equivalent method compared to the SC assessment despite increasing variability of the measurements. Differences between atrophy assessment on individual MRI segmentation and registration-based atrophy estimation were described not only in the study underlying the FSL-SIENA(X) method itself [32], but also in a review comparing different methods to assess whole brain atrophy [33], and in the study describing the recently proposed registration-based measurement of SC atrophy [34]. In summary, indirect atrophy calculation from segmentation at each time point is introducing greater variabilities, because differences in intensity scales, for example, are not taken into account, and it increases the noise because of inconsistent segmentation of the same brain regions. Thus, segmentation-based methods are less reliable for longitudinal atrophy quantification compared to registration-based approaches [35].

In our study, Gd+ lesions seemed to have no effect on atrophy rates of the brain. This indicates that diffuse inflammatory processes in the brain parenchyma gave rise to the observed PA effects rather than localized breakdown of the blood–brain barrier in Gd+ lesions. This seemed to be unintuitive at first glance, as contrast-enhancing lesions constitute active inflammatory processes and should therefore show the most pronounced dissolution of inflammation resulting in PA. Other studies reported that BL inflammatory status demonstrated by the presence of Gd+ lesions had an impact on brain volume atrophy rates in patients treated with interferon-beta or natalizumab [12, 36]. However, their patient groups had higher grades of disability, longer disease durations, and considerably higher percentages of Gd+ lesions (>50%) compared to our study (20%). Our study population consisted of very early MS or CIS patients with low overall disability and brain lesion loads. In conclusion, Gd+ lesions may not necessarily drive PA, and other mechanisms seem to exist.

Likewise, the presence of T1-hypointense lesions in the cervical cord had no considerable effect on the detected SC atrophy rates. This may support the hypothesis that diffuse processes are involved in the PA effect observed following interferon-beta initiation rather than a direct influence of the lesions. Although T2 cervical lesion load was not quantified in our study, previous investigations demonstrated correspondence between T1 and T2 lesions in SC [37], so this might be transferable. Furthermore, Gd enhancement in the upper cervical cord was negligible, and thus had no considerable impact on the SC atrophy rates in our study.

Limitations

In this study, we included both CIS and early RRMS patients in the interferon-beta-treated and -untreated patient groups. Whereas several studies reported SC atrophy in CIS and early RRMS patients [38], others did not find differences in SC atrophy between healthy controls and CIS patients but did between controls and MS patients [27]. In another study, no significant atrophy progression in patients with a remaining diagnosis of CIS after 5 years was observed [39]. The inclusion of CIS patients, who potentially show less atrophy progression than patients with definite MS, could lead to lower atrophy rates in a mixed group of CIS and RRMS. Because similar proportions of treated and untreated patients in the CIS and RRMS subgroups were observed, our findings of considerably faster SC atrophy progression during the first year in the group of interferon-beta-treated patients support our hypothesis of a manifest PA effect in SC.

Based on the results of studies that have addressed the PA effect in the brain, it would be interesting to perform MRI examinations after therapy initiation at intervals shorter than once per year for a detailed characterization of the PA effect in SC. Although different studies also showed PA in the brain using 12-month data [36], recent studies proposed that brain PA is occurring mostly during the first 6 months [40], which we cannot confirm and transfer to SC with annual MRI data. However, our results emphasize the existence of PA in the brain and in the SC even with such a relatively rough temporal resolution, and may constitute the basis for further, more detailed longitudinal studies.

Regarding technical limitations of this study, dedicated longitudinal methods for the assessment of SC atrophy rates should preferably be used in future studies. Recently developed registration-based methods for measuring longitudinal volume changes could increase reliability [34, 41].

To uncover tissue-dependent mechanisms of PA, GM and WM atrophy rates should be considered longitudinally in prospective

studies in addition to our whole brain and MUCCA atrophy rates. In a recent study, the yet unreleased extension SIENA-XL was used to study brain PA in RRMS separately for GM and WM, which was found to affect predominantly GM [40]. In our study, cross-sectionally calculated GM and WM atrophy rates yielded a more pronounced PA effect for WM, although a trend for GM also existed, which would be worth further investigation by use of a more reliable, longitudinal method. Similarly, it would be of great importance to analyze GM and WM in SC. Toward this, dedicated SC MRI would be necessary to use established methods for GM and WM differentiation [42].

CONCLUSIONS

Overall, our results provide evidence for a PA effect not only in the brain but also in the upper cervical cord. This important effect must be considered when SC atrophy is used as a biomarker for monitoring treatment effects in MS. Further studies are warranted to explore the PA effect in the SC in greater detail, among different DMTs and furthermore between spinal GM and WM.

AUTHOR CONTRIBUTIONS

Britta Matusche, Barbara Bellenberg, Ralf Gold, and Carsten Lukas contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. Britta Matusche, Barbara Bellenberg, and Carsten Lukas contributed to drafting the text or preparing the figures. Ralf Gold and Carsten Lukas acquired funding.

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CONFLICT OF INTEREST

R.S. has received consulting and speaking honoraria from Biogen Idec and Roche Pharma, and has received research scientific grant support from Novartis Pharma. V.P. has received research support from Novartis (Oppenheim Förderpreis). A.B. received consulting and/or speaking fees from Alexion, Bayer HealthCare, Biogen, Celgene, and Roche. His institution has received compensation for clinical trials from Alexion, Biogen, Merck, Novartis, Roche, and Sanofi, all outside the present work. F.Z. has received research grants and/or consultation funds from Biogen, Federal Ministry of Education and Research (BMBF), Bristol-Myers Squibb, Celgene, German Research Foundation (DFG), Janssen, Max Planck Society, Merck Serono, Novartis, Progressive MS Alliance, Roche, Sanofi Genzyme, and Sandoz. S.G.M. has received honoraria for lecturing and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer HealthCare, 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 BMBF, DFG, Else Kröner Fresenius Foundation, German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies Münster, German Neurology Foundation, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, Merck Serono, Novartis, ONO Pharma, Roche, and Teva. F.W. has received honoraria from Genzyme, Novartis, Teva, and Biogen for speaking or for serving on a scientific advisory board, a travel grant for attending a scientific meeting from Merck Serono and Novartis, and grant support from Merck Serono, Novartis, and the BMBF (Projects Biobanking and Omics in ControlMS as part of the Competence Network Multiple Sclerosis). R.A.L. has received compensation for serving as a consultant or speaker from Biogen, Celgene/BMS, Genzyme/Sanofi, Janssen, Merck Serono, Novartis, and Roche; and has received research support from Biogen Idec and Novartis. T.K. has received speaker honoraria and/or personal fees for advisory boards from Bayer HealthCare, Novartis Pharma, Roche Pharma, Alexion/AstraZeneca, and Biogen. The institution she works for has received grant support for her research from Bayer Schering, Novartis, and Chugai Pharma in the past. R.G. has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis, and Teva Neuroscience. He, or the institution he works for, has received research support from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis, and Teva Neuroscience. He has also received honoraria as a journal editor from SAGE and Thieme Verlag. C.L. has received consulting and speaking honoraria from Biogen Idec, Bayer Schering, Daiichi Sankyo, Merck Serono, Novartis, Sanofi, Genzyme, and Teva. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Patients' raw MRI and clinical data cannot be made available due to data protection regulations. Other data can be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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