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Reduced brain volumes in children with radiologically isolated syndrome

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Abstract

Background: Pediatric multiple sclerosis (MS) is associated with reduced brain volumes at first episode compared to healthy controls.

Objective: To assess brain volumes in children fulfilling the criteria of radiologically isolated syndrome (RIS) at onset and over time.

Methods: Clinical course, laboratory findings, MR-imaging in pediatric RIS were compared to controls from the NIH Pediatric MRI Data Repository and a cohort of patients with pediatric MS.

Results: 20 RIS and 37 MS patients were included in the study. Median age at RIS diagnosis was 13.1 years (IQR: 10.3, 14.8) and whole brain volume was reduced by 77 cm^3, compared to matched healthy controls (1673 cm^3 (1637, 1728) vs 1750 cm^3 (1699, 1802)). Nine RIS patients developed MS (RIS-to-MS) at a median age of 15.8 years (12.7,17.0). Longitudinal volumetry revealed lower brain volume in both non-converting and converting RIS patients compared to controls, similar to the trajectory in pediatric MS (RIS −4.7% (−6.5, −2.9), RIS-to-MS −5.1% (−6.9, −3.4), MS −6.6 % (−7.6, −5.5)). Oligoclonal bands, cerebrospinal fluid (CSF) pleocytosis, and reduced brain volume in RIS at diagnosis increased hazards of conversion to MS.

Conclusions: Reduced whole brain volume is already present in pediatric radiologically isolated syndrome (RIS). Longitudinal analysis of RIS patients revealed reduced brain volume over time, similar to MS.

Keywords: pediatric radiologically isolated syndrome, pediatric multiple sclerosis, MR-volumetry

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Introduction

Radiologically isolated syndrome (RIS) is defined by the presence of incidental white matter lesions highly suggestive of multiple sclerosis (MS) in a brain MRI scan but without clinical symptoms typical of MS.[1]

Adults with RIS have a 34% risk of developing MS within the next 5 years. Factors associated with an increased hazard for the conversion to MS are young age, spinal cord involvement, infratentorial lesions, presence of oligoclonal bands (OCBs), and male sex.[2,3] Recent volumetric studies found that adults with RIS already suffer from brain volume loss which is particularly prominent in subcortical structures such as thalamus.[4–6] The treatment of adult RIS patients is still debated, but there are recent clinical trials suggesting the potentially beneficial effects of disease-modifying treatment (DMT) with dimethyl-fumarate or teriflunomide.[5,6]

Current recommendations for the diagnosis of pediatric RIS include the presence of incidental brain MRI lesions in the white matter with well-circumscribed T2 hyperintensities (⩾3 mm) that fulfill the 2010 McDonald criteria for dissemination in space (DIS) and are not consistent with a vascular pattern.[7] In an international cohort of 38 children fulfilling the criteria of RIS, 42% developed definite MS within a median time of 2.0 years.[7] Risk factors for clinical conversion were—similar to adult RIS patients, the presence of OCBs in the cerebrospinal fluid (CSF) and spinal cord lesions. Overall, pediatric patients

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with RIS showed faster clinical and radiological activity when compared to adults.[3,7]

Pediatric MS patients show an increased disease activity with more relapses at the beginning of the disease[8,9] and have a reduction in whole brain volume already at first clinical presentation.[10]

The aim of the current study was to assess if whole brain volumes and volume of substructures are reduced in pediatric RIS patients when compared to healthy controls and children with MS. Investigating the evolution of whole brain volume in these patients could be useful and clinically relevant in identifying high risk patients for converting to MS.

Materials and methods

Pediatric RIS patients were included retrospectively from five different hospitals (Children's Hospital Datteln, Witten/Herdecke University, Datteln, Germany; Olgahospital, Stuttgart, Germany; Medical University of Vienna, Austria; Birmingham Women's and Children's Hospital, United Kingdom; Children's Hospital Augsburg, Germany). Inclusion criteria were the diagnosis of pediatric RIS according to the criteria proposed by Makhani et al.[7] All children had cerebral MRI studies including a high-resolution 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence at the time of diagnosis as well as clinical information including medical history, clinical examination, laboratory findings including CSF cell count and OCBs, start of a disease modifying therapy and clinical follow-up. RIS patients lacking clinical details or MRI without MPRAGE sequences were excluded from the study.

MRI data from RIS and RIS-to-MS patients and from 37 children with MS at baseline and at 2 years follow-up[10,11] were compared to MPRAGE sequences of matched healthy controls derived from the NIH Pediatric MRI Data Repository. The NIH repository was created by the NIH MRI Study of Normal Brain Development as a multi-site, longitudinal study of healthy and normally developing children conducted by the Brain Development Cooperative Group (MRI scans acquired at 1.5 T).[11] Regarding the MS patients, MS was diagnosed according to the criteria of the International Pediatric Multiple Sclerosis Study Group (IPMSSG).[12]

Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committee of the University Witten/Herdecke, Germany, and by South Birmingham Research Ethics Committee, UK. All caregivers provided written informed consent.

MRI data acquisition and analysis

All patients had a baseline high-resolution MPRAGE cerebral MRI sequence without contrast agent at the time of RIS diagnosis. A total of 31 follow-up scans were available from 14 out of 20 RIS patients over a median observation time of 2.0 years (IQR: 1.1; 3.2). The most common reason for obtaining an MRI scan was headache 65% (13/20 patients), migraine 10% (2/20 patients) followed by vertigo 15% (3/20 patients), seizures 10% (2/20 patients), uveitis 5% (1/20 patients), anorexia nervosa 5% (1/20 patients), and attention deficit disorder 10% (2/20 patients).

MRI data were compared with healthy controls from the NIH Pediatric MRI Data Repository and with MRI data from patients with MS at baseline and at 2 years follow-up that has previously been reported.[10,11] T1 MPRAGE and FLAIR MRI sequences were linearly co-registered, and MPRAGE images were brain-extracted to generate a white matter (WM) mask. Automatic lesion segmentation was performed on FLAIR images using the LST toolbox (version 2.0.15) for SPM. The lesion and WM masks, along with the original MPRAGE images, were processed with the FSL lesion filling tool to prepare images for volumetric analysis. Finally, brain volumes (normalized for head size) were estimated from the lesion-filled T1 MPRAGE images using the Structural Image Evaluation with Normalization of Atrophy Cross-sectional (SIENAX)[13] package and the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Integrated Registration and Segmentation Tool (FIRST), both part of the FMRIB Software Library (FSL).[13–15] FSL SIENAX provides estimates for whole brain, gray matter, cortical gray matter, white matter, and ventricular CSF (vCSF) volumes. FSL FIRST was applied to analyze thalamus volumes.

Statistical analysis

Descriptively, we report absolute and relative frequencies for categorical variables, median with range or interquartile range (IQR) for continuous variables, stratified by patient group (controls, MS, RIS; controls, MS, RIS, RIS-to-MS). Trajectories of brain volumes by patient groups are visually displayed in scatterplots along with a locally estimated scatterplot smoothing (LOESS). Matching of patient observations to healthy controls (HC) is based on age (±1 year) and sex, based in a 1:5 ratio. Brain volumes by matched patient groups are displayed using boxplots.

Table 1. Summary of baseline clinical characteristics of pediatric patients with RIS and MS who were enrolled in the study.

	RIS ($n=20$)	MS ($n=37$)	Total ($n=57$)
Gender			
Female	16 (80.0%)	18 (48.6%)	34 (59.6%)
Male	4 (20.0%)	19 (51.4%)	23 (40.4%)
Age at first MRI			
Median (IQR)	13.1 (10.3, 14.8)	14.8 (14.4, 16.3)	14.6 (13.5, 16.0)
Spinal lesions			
No	11 (55.0%)	10 (27.0%)	21 (36.8%)
Not performed	3 (15.0%)	7 (18.9%)	10 (17.5%)
Unknown	0 (0.0%)	6 (16.2%)	6 (10.5%)
Yes	6 (30.0%)	14 (37.8%)	20 (35.1%)
OCBs			
No	3 (15.0%)	5 (13.9%)	8 (14.3%)
Not performed	2 (10.0%)	0 (0.0%)	2 (3.6%)
Yes	15 (75.0%)	31 (86.1%)	46 (82.1%)
Missing	0	1	1
CSF cell count			
Median (IQR)	4.0 (0.0, 11.8)	7.5 (1.2, 14.8)	6.0 (0.0, 14.0)
Unknown	0	3	3
CSF cell count			
$\leqslant 5$	10 (50.0%)	14 (41.2%)	24 (44.4%)
>5	10 (50.0%)	20 (58.8%)	30 (55.6%)
Missing	0	3	3

RIS: radiologically isolated syndrome; MS: multiple sclerosis; MRI: magnetic resonance imaging; IQR: interquartile range; CSF: cerebrospinal fluid.

Linear mixed effects models with fixed effects of MRI field strength and random intercepts are used to account for the matching—where mean absolute or relative differences between matched patients and controls are derived, along with 95% confidence intervals (CIs). Within the subset of the 20 RIS at baseline patients, we model factors potentially associated with the time to MS conversion using a Bayesian time-to-event model, with and without adjustment for the respective other factors. This approach was chosen due to the strong limitations in the number of events, which is why any results have to be considered exploratory. We derive Hazard Ratio (HR) estimates along with 95% credibility intervals (CrI), based on models fitted with default priors, and eight chains, each with 1000 iterations. The mixing of chains and the posterior distribution were visually evaluated, all models converged (Rhat = 1) without divergent transitions.

For all analyses R[16] and additional R packages were used.[16–21]

Results

A total of 20 patients fulfilling the criteria of pediatric RIS were included in the study.[7] The median age of the patients at time of RIS diagnosis was 13.1 years (IQR 10.3, 14.8, 17 females). At presentation OCBs were detected in 15/18 patients, the median CSF cell count was 4.0 (IQR 0.0, 11.8) and 10/20 patients (50%) had a cell count $>5/\mu L$. On the initial cerebral MRI scan, 10/20 RIS patients (50%) had $\geqslant 10$ brain lesions, and 10 patients had <10 lesions. Seventeen RIS patients (85%) underwent a spinal MRI of whom six had spinal lesions (Table 1).

Eight patients in the RIS-to-MS group were administered DMT after conversion. Two patients received interferon-beta, two were treated with teriflunomide, two with dimethyl fumarate, and two with fingolimod. Treatment changes including escalation was necessary in six patients: two patients escalated to fingolimod and another two to teriflunomide. One patient who was started on fingolimod, was escalated to natalizumab, and finally to ocrelizumab. Another patient treated with

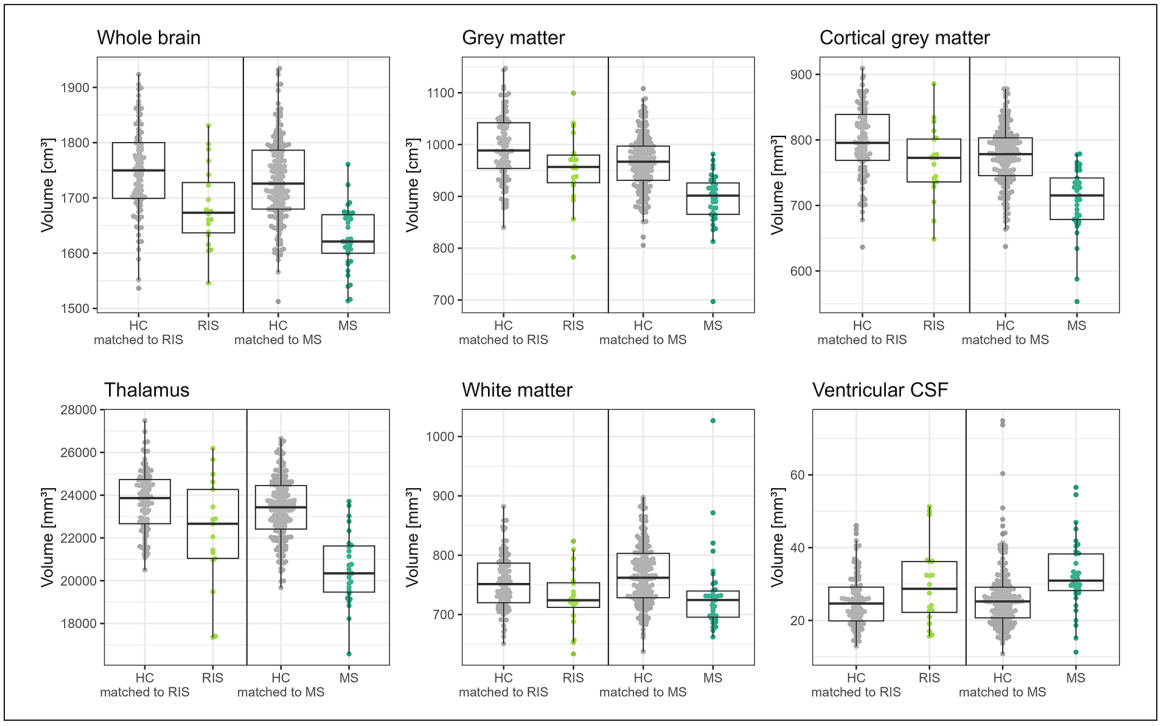

Figure 1. Baseline brain volume loss in RIS and MS.
Brain volume measurements at time of onset in RIS, MS, and respective matched healthy controls (HC). RIS patients who developed MS showed more brain atrophy at time of RIS diagnosis when compared to healthy controls.

fingolimod received subsequently natalizumab. None of the patients received treatment with either methylprednisolone or DMT prior to conversion.

RIS patients show global and regional brain atrophy already at the time of diagnosis

Whole brain volume in RIS patients at the time of RIS diagnosis is reduced by 76.6 cm^3 compared to matched HC [median (IQR) 1673.2 cm^3 (1636.8, 1727.8) vs 1749.8 cm^3 (1699.2, 1800.1); Figure 1, Supplemental Table 1]. Similarly, gray matter, cortical gray matter, white matter, and thalamus are also reduced, and ventricular volume is increased compared to matched HC (Figure 1 and Supplemental Table 1). In comparison, median brain volume in MS patients at the time of first presentation (and MS diagnosis) before treatment is 104.8 cm^3 lower compared to matched controls [1621.1 cm^3 (1599.9, 1669.5) vs 1725.9 cm^3 (1679.8, 1786.0)] (Figure 1 and Supplemental Table 1).

RIS patients show reduced global and regional brain volumes over time

Longitudinal volumetric analyses revealed reduced brain tissue volumes over time in RIS and MS patients compared to HC (Figure 2).

Whole brain volume in RIS patients over time is −87.9 cm^3 lower (95% CI: −120.1, −55.6) or −4.8% (−6.7, −3.0) compared to matched HC (Figure 3). In comparison, whole brain volume in MS patients is −116.7 cm^3 (−135.0; −98.4) or −6.6 % (−7.6, −5.5) lower compared to HC. Similarly, gray matter, cortical gray matter, thalamus, and white matter volumes are reduced both in RIS and MS patients over time compared to HC with a stronger reduction in MS patients. In line with this, ventricular volume is increased in both RIS and even more in MS patients.

Both RIS and RIS-to-MS patients show reduced brain volumes over time

Over time, 9/20 RIS patients converted to MS (RIS-to-MS): the median age at initial RIS diagnosis in these patients was 13.7 years (IQR: 10.4, 15.1) and 15.8 years (IQR: 12.7, 17.0) at time of MS diagnosis with a median time to MS conversion of 3.3 years (95% CI: 2.6–NA; Supplemental Figure 1). Of these, 7/9 (77.8%) patients had ⩾10 lesions in the first MRI at RIS diagnosis and 6/9 (66.7%) patients had a CSF cell count >5 cells/µL. The clinical characteristics comparing RIS-to-MS and non-converting RIS patients are shown in Supplemental Table 2.

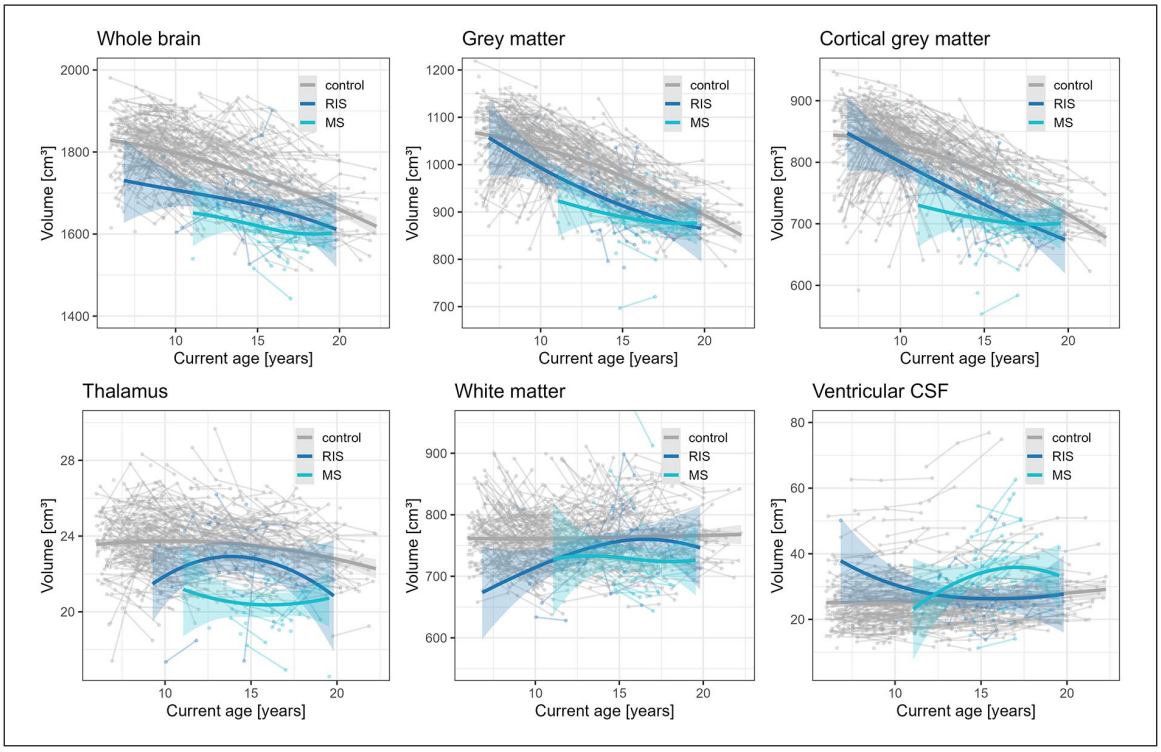

Figure 2. Brain Volume over time in RIS and MS patients.
RIS patients show reduced global and regional brain volumes over time. Models for whole brain, white and gray matter are modeled using a degree 3 spline for age at MRI, models for vCSF and thalamus use a linear effect of age at MRI only; all models additionally include age at baseline (linear) and gender.

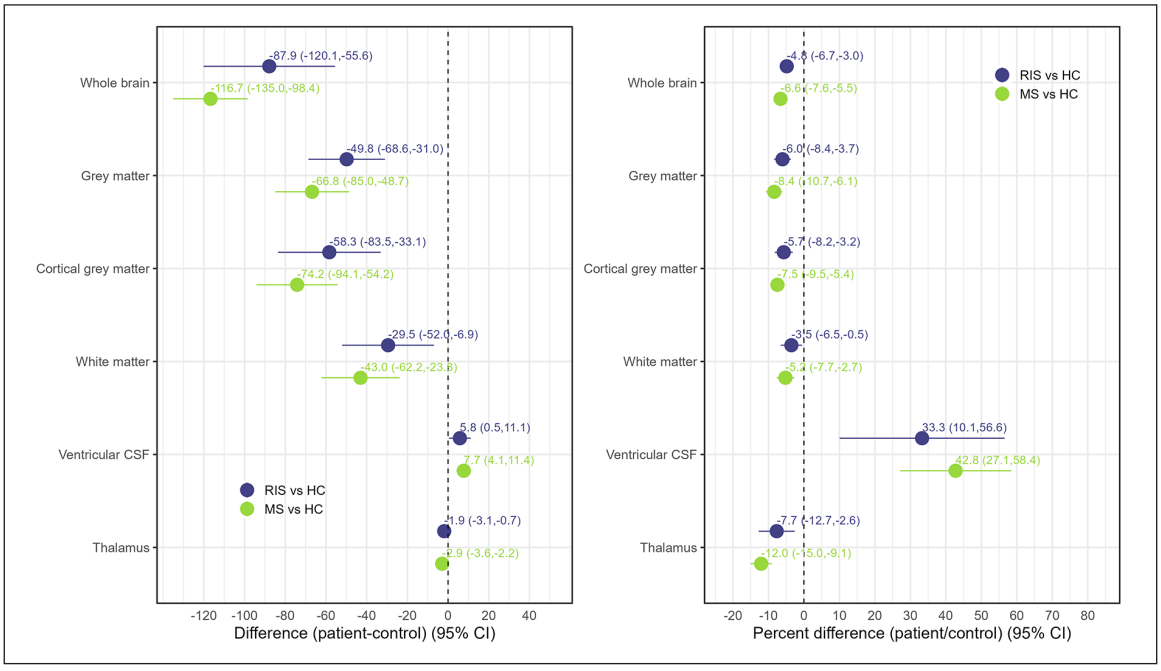

Figure 3. Brain Volume over time in RIS and MS patients.
Brain volumes are reduced both in RIS and MS patients over time compared to HC with a stronger reduction in MS patients. Effect estimates derived from linear mixed models, based on matching by age (±1 year) and sex, showing a. absolute difference between patients and controls (in mm^3) and b. relative difference between patients and controls (in %); 95% confidence interval (CI).

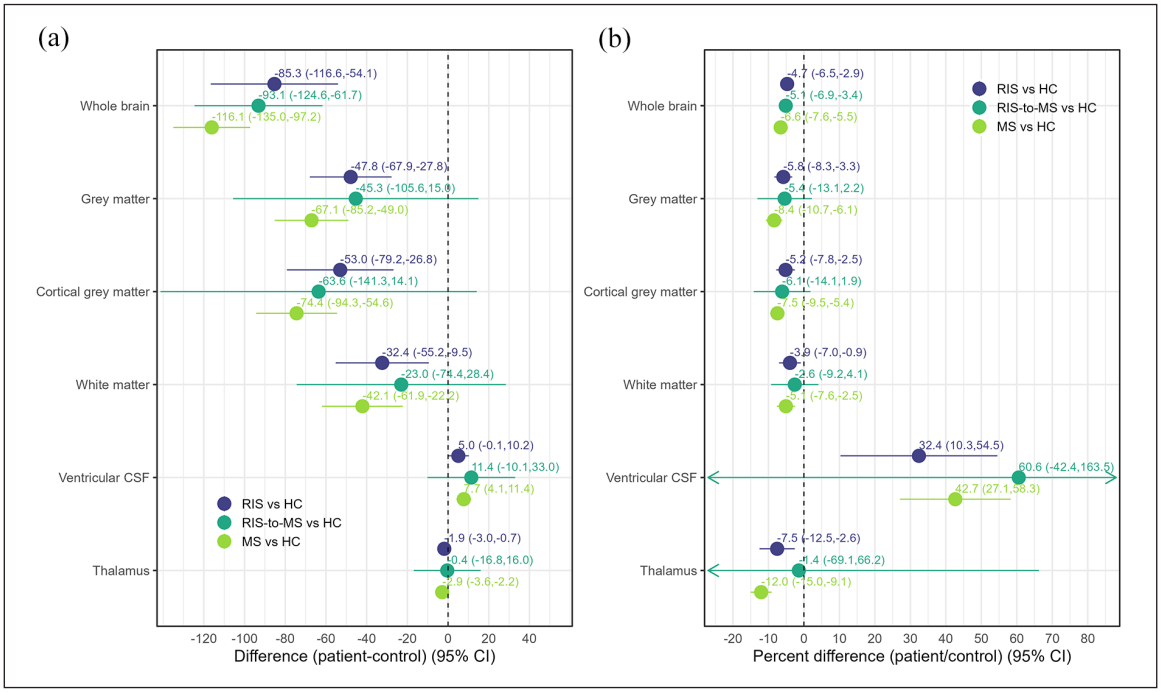

Figure 4. Comparison RIS versus RIS-to-MS.
Both RIS and RIS-to-MS patients also show reduced brain volumes over time when compared to MS. Effect estimates derived from linear mixed models, based on matching by age (±1 year) and sex, showing (a) absolute difference between patients and controls (in mm^3) and (b) relative difference between patients and controls (in %); 95% confidence interval (CI).

When comparing RIS patients who developed MS (RIS-to-MS) and RIS patients who did not develop MS over a median observation time of 2.0 years (IQR: 1.1; 3.2) using linear mixed models, both show lower brain volume over time compared to healthy controls: −4.7% (95% CI: −6.5; −2.9) or −85.3 cm^3 (−116.6; −54.1) in RIS patients and by −5.1% (−6.9; −3.4) or −93.1 cm^3 (−124.6; −61.7) in RIS-to-MS. In comparison, whole brain volume in MS patients was −6.6% (−7.6; −5.5) or −116.6 cm^3 (−135.0; −97.2) lower than in HC. Moreover, gray matter, cortical gray matter, thalamus, and white matter volumes were similarly lower in both RIS and RIS-to-MS patients. MS patients consistently showed more pronounced volume deficit compared to both RIS and RIS-to-MS patients, while RIS-to-MS patients resulted in similar gray matter and thalamic volumes and more pronounced lower cortical gray volumes compared to RIS patients (Figure 4).

RIS patients who developed MS showed more brain atrophy at time of RIS diagnosis

Assessing the baseline MRI brain volumes in RIS patients who later develop MS (RIS-to-MS) compared to patients who did not develop MS by the end of the observation period (RIS), RIS-to-MS patients already had lower brain volume compared to RIS patients with a consistent pattern of lower absolute whole brain volumes going from RIS to RIS-to-MS to MS compared to their matched HC, respectively (Supplemental Figure 2 and Supplemental Table 2).

Risk factors in RIS patients for MS diagnosis

Using Bayesian time-to-event models, we investigated variables potentially associated with time to MS diagnosis. Given the low sample size of 20 RIS patients at first visit and the low number of nine patients who subsequently developed MS, these findings should be considered exploratory and in light of the high degree of uncertainty. Keeping this in mind, our data suggest that the hazards for an MS diagnosis may increase with the presence of OCBs and a CSF cell count >5 cells/µL at time of diagnosis. Furthermore, higher brain volumes at time of diagnosis may reduce the hazards of MS diagnosis, just as spinal cord lesions at time of RIS diagnosis in our cohort, which is contrary to previous reports (Figure 5).[7]

Discussion

In the current study, we observed that (1) brain volume is already lower in children with RIS at time of

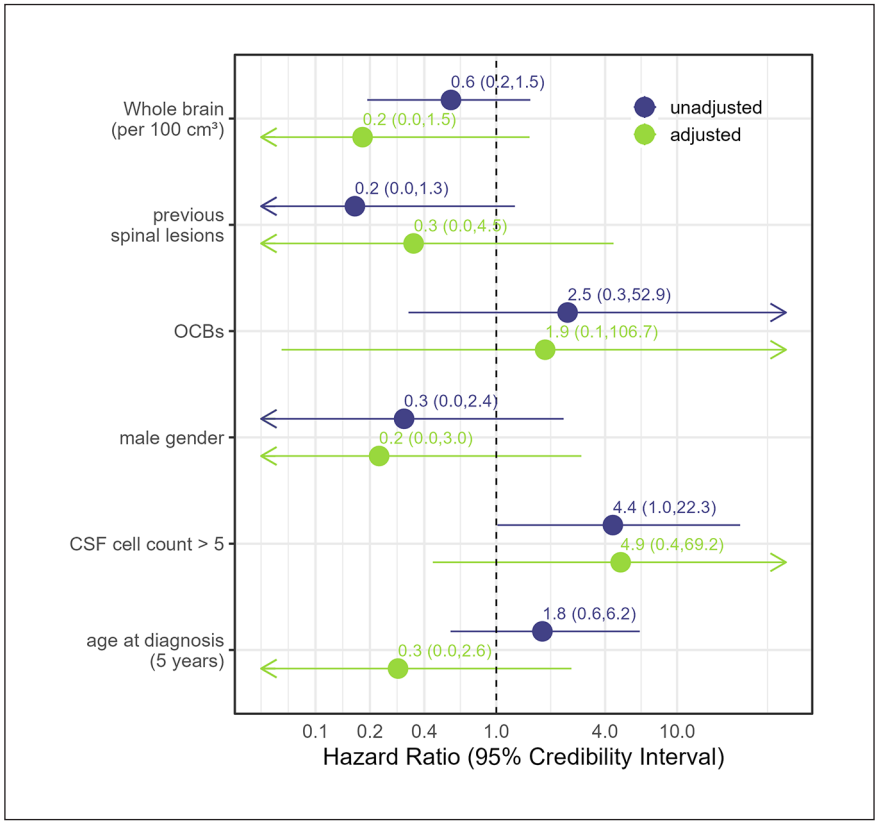

Figure 5. Risk factors for conversion to MS.
OCBs and increased CSF cell count at RIS diagnosis increase the hazards for an MS diagnosis. A Bayesian time-to-event model for the time to MS conversion, including different risk factors, hazard ratio estimates derived from a univariable (unadjusted) or multivariable (adjusted) model.

diagnosis and that (2) RIS patients who later developed MS had even more pronounced lower brain volume at the time of RIS diagnosis compared to non-converting RIS patients.

RIS has recently gained attention because it offers an opportunity to gain insight into the initial phase of MS. It is known that adult patients with RIS have a higher risk for developing MS in the presence of factors like younger age, spinal cord involvement, infratentorial MRI lesions, and OCBs.[2,3] A recent prospective cohort study found that patients who did not fulfill the 2009 RIS criteria had a similar risk of developing a clinical event 5 years after the index MRI when additional risk factors are present (spinal cord lesions and OCBs).[22]

In previous studies with adult RIS patients, volumetric analyses of brain subregions identified a decrease in global cortical volume and regional cortical thinning in the frontal and temporal lobes.[23] In addition, significant volume reductions were observed in thalamic volumes, as well as cerebellar white matter and anterior cerebellar gray matter.[24,25] The present study provides evidence that reduced whole brain volumes in addition to tissue loss in different subregions including cortical gray matter, white matter, and thalamus does occur already at time of RIS diagnosis in children compared to healthy controls.

We further show that RIS patients experience persistently lower brain volume over time which is in line with studies in adult RIS patients.[4–6,26] Furthermore, we identified a subgroup of children who later developed MS (RIS-to-MS) and who had an even more pronounced whole brain volume loss at time of RIS diagnosis. The volume loss of RIS-to-MS patients was similar to the results obtained in pediatric MS patients at time of first clinical event.[10]

In our study, children with RIS had MS laboratory characteristics including CSF-restricted oligoclonal bands and CSF pleocytosis. Based on a Bayesian model, we show that the presence of OCBs and CSF pleocytosis at time of diagnosis in RIS patients is indeed associated with increased hazards for a

conversion to MS. This finding is in accordance with another pediatric RIS cohort where positive OCBs were associated with the conversion to MS.[27]

Treatment of patients, particularly with risk factors associated with conversion to MS, is currently under debate. First clinical trials in adult RIS patients reported a benefit of treatment, resulting in relevant reduction of risk for a first clinical demyelinating event.[5,6] At present treatment of pediatric RIS patients with DMTs is not recommended. Our data of brain volume loss observed already in children with RIS and the upcoming revision of the McDonald criteria 2017 supports the timely administration of DMTs. According to the new recommendations, adult RIS patients fulfilling DIS and DIT of the McDonald criteria 2017 or DIS and additional positive OCBs can be diagnosed with MS. In our cohort 18/20 children (90%) met the DIS 2017 criteria at first MRI and 14/20 RIS patients met the criteria for both DIS 2017 and presence of OCBs and could have been in retrospect diagnosed with MS. Of these, 7/14 patients (50 %) converted to MS as described and 7/14 patients remained RIS within a median follow up time of 1.7 (range: 1.0–4.0) years.

In the pediatric MS cohort, DMT treatment was initiated after MS manifestation. In the follow up analysis within the first two years including 21 patients, 13/21 patients (61.9%) were treated with DMTs. In particular, 10/13 children received interferon beta (two escalated to natalizumab and one switched to glatiramer acetate) and 3/13 children were treated with natalizumab without previous first-line therapy.[10] However, brain volumetric analyses showed -as expected, in particular for interferon beta- no relevant differences in brain volume at follow-up between patients with and without DMT.[10] This finding may reflect that neuroinflammatory damage precedes clinical manifestation and highlights the potential value of early therapeutic intervention in pediatric patients with RIS.

Pediatric onset MS patients have a longer time window before they develop an EDSS greater than 4, nevertheless disease activity even in the initial phase of the disease already leads to clinical manifestations such as fatigue, depression, learning disabilities even at a young age when compared to adult-onset MS.[8] Therefore, it is of utmost importance to identify children at risk and collect evidence of ongoing brain injury early. Within our cohort, eight patients from the RIS-to-MS group initiated DMTs after conversion, with six of these individuals necessitating subsequent treatment escalation. Despite the limited sample size, this finding together with the progression of brain volume loss underscore the importance of early consideration of DMT initiation in pediatric patients with RIS, with the aim of preventing or postponing the need for escalation to more intensive therapeutic regimens.

The following limitations of our study need to be addressed. First, we studied a relatively small sample size of RIS patients, in particular, when comparing patients with RIS versus RIS-to-MS. Second, we did not directly match nor compared RIS and MS patients. Given the limited sample size in the patient groups, we restricted the analyses to comparisons between each patient group (MS and RIS, or MS, RIS, and RIS-to-MS, respectively) and the matched healthy control group. Future studies with larger cohorts will be necessary to directly assess differences between MS and RIS patients while still matching for age and sex. Another limitation is that harmonization for scanner or site variability in this multicenter study was limited by small sample sizes per site and confounding between sites and groups (controls and patients measured at different scanners). Furthermore, because of the multicenter and retrospective design of the study, not all patients received a spinal cord MRI or a follow-up MRI scan. Finally, other risk factors for predicting the conversion of RIS to MS such as serum and/or CSF neurofilament light or the central vein sign were not part of this study.

Conclusion

This study highlights that reduced brain volume is already evident at time of RIS diagnosis in children, with more pronounced volume reductions in those who later develop multiple sclerosis (RIS-to-MS). While treatment options for pediatric RIS remain under debate, ongoing trials in adult RIS patients may provide valuable insights into potential therapeutic strategies. A deeper understanding of the early stages of MS progression will aid in improving early diagnosis, risk stratification, and intervention strategies for pediatric RIS.

Data Availability Statement

The data included in the current study are available from the corresponding author on request.

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: G.K. has nothing to declare. F.B. has nothing to declare. A.T. has nothing to declare. A.A. has nothing to declare. R.C. has nothing to declare. E.-M.W. has received

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Supplemental Material

Supplemental material for this article is available online.

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