Neurite orientation dispersion and density imaging discloses early changes in the normal-appearing white matter in paediatric multiple sclerosis

INTRODUCTION

Paediatric multiple sclerosis (pedMS) brain is known to be impacted by heightened inflammation and axonal degeneration.[1] Structural changes in the normal-appearing white matter (NAWM) of pedMS have been disclosed by diffusion tensor imaging, further emphasising that MRI visible white matter (WM) lesions do not capture the full extent of tissue damage in MS.[2] Understanding of the complexity of early brain pathology in pedMS can help to better characterise the relationship between inflammation and neurodegeneration in MS.

Neurite orientation dispersion and density imaging (NODDI), a multicompartment model of diffusion MRI, is a clinically feasible method for better capturing brain microstructural complexity in vivo.[3] Specifically, NODDI provides quantitative measures including the neurite density index (NDI), considered a measure of neurites (ie, axons and dendrites) volume and orientation dispersion index (ODI), reflecting neurite orientation variability.

In this exploratory study, we applied NODDI to investigate the presence of early microstructural damage in pedMS compared with a matched group of healthy controls (HC), and its correlation with physical disability and WM lesion volume (LV) within tracts. A list of the acronyms used throughout the manuscript is provided in online supplemental table 1).

MATERIALS AND METHODS

Subjects

Nineteen relapsing-remitting pedMS patients (aged ≤17 years) were prospectively enrolled in a single MS Centre between January 2019 and April 2021. Eight patients were treatment naïve; the remaining patients were in stable treatment with natalizumab. The median number of infusions at the time of MRI scan was 12 (IQR, 6–20). Twelve HC, balanced by age and sex, with no previous history of neurological dysfunction and a normal neurological examination, were also evaluated (see the online Supplemental Methods for pedMS inclusion criteria). All subjects underwent a detailed neurological evaluation, including Expanded Disability Status Scale (EDSS) score, within 1 week from the MRI acquisition.

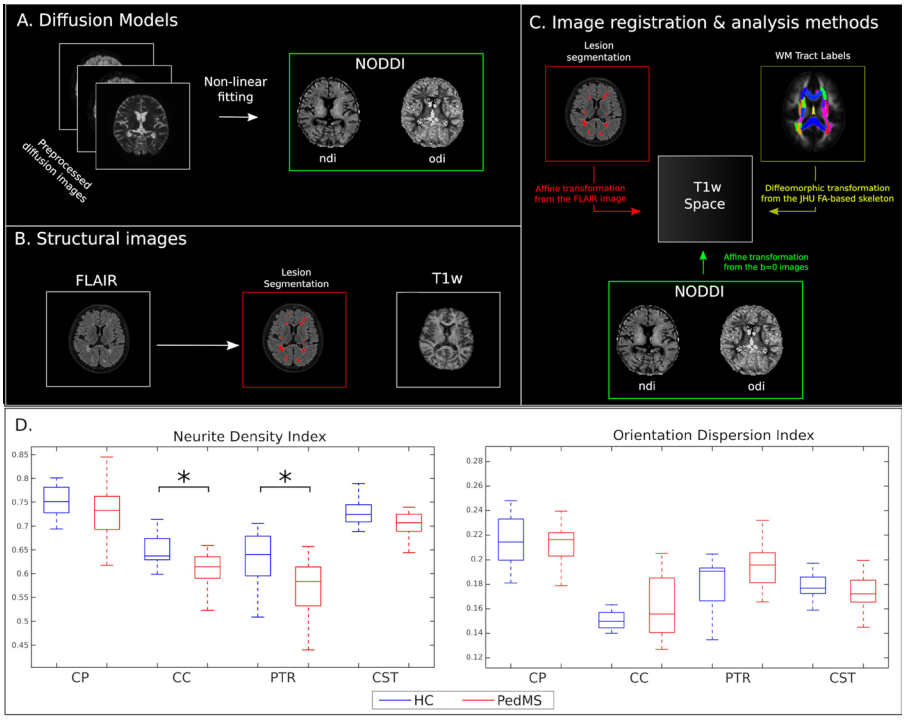

Figure 1 General overview of the acquired images, their processing and main results. (A) Microstructural parameters quantified on diffusion-weighted images. (B) Structural images and lesion segmentation. (C) Registration details for each image necessary to perform the tract-wise assessment of NAWM damage. (D) Box plots highlighting group differences in NODDI metrics in the different tracts. Significant differences ($p<0.05$)—adjusted for age and gender—are highlighted by *. The adjusted p-values for CC NDI and PTR NDI are 0.175 and 0.011, respectively. CC, corpus callosum; CP, cerebellar peduncle; CST, corticospinal tract; FLAIR, fluid-attenuated inversion recovery; HC, healthy controls; NAWM, normal-appearing white matter; NDI, neurite density index; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; PedMS, paediatric multiple sclerosis; PTR, posterior thalamic radiation.

MRI

The following sequences were acquired during a 3T whole-brain MRI scan: sagittal three-dimensional (3D) T1-weighted turbo field echo; sagittal 3D fluid-attenuated inversion recovery (FLAIR). To investigate microstructural abnormalities using the NODDI model, the diffusion protocol was adapted from Zhang *et al*.[3] T2-hyperintense lesions were identified by the consensus of two observers on FLAIR scans using manual segmentation (ITKSNAP), yielding the total and tract-specific WM LV and the lesion mask. Diffusion MRI data were initially denoised and corrected for eddy current effects, involuntary movement and B0 field inhomogeneities. NODDI (NDI and ODI) maps were quantified on preprocessed diffusion images. Regions of interest analysis was performed to investigate group differences and tissue-specific microstructural damage in the corpus callosum (CC), posterior thalamic radiation (PTR), which includes optic radiation, cerebellar peduncle (CP) and corticospinal tract (CST) (figure 1A–C).

Median values of the different NODDI metrics were then extracted from patients NAWM and HC WM of the aforementioned tracts, along with tract-specific LV. Online supplementary material contains additional information regarding sequence geometry, image registration and model quantification details.

Statistical analysis

Continuous and categorical variables were reported as mean (SD) and frequencies, respectively. Differences in age and sex were assessed using a two-sample t test and χ^2 test. NODDI measures in the NAWM of the different tracts were compared between HC and pedMS using non-parametric multivariate analyses of variance, including age and sex as covariates. Significance was assessed by 10 000 random sign-flip.[4] The p-values were further corrected for multiple testing using resampling-based min-p procedures. The relationship between clinical findings and MRI metrics was investigated using Spearman's rank correlation. Analyses were performed using SPSS (V.23.0) and R Software (R Core Team (2019)) with package flip (https://CRAN.R-project.org/

package=flip). Statistical significance was set at <0.05.

RESULTS

PedMS and HC did not differ in age and sex (p=0.1 and p=0.2, respectively) (see online supplemental table 2). Compared with HC, pedMS showed significantly lower NDI values in the CC (p=0.029; p=0.175 corrected) and in the PTR (p=0.001; p=0.011 corrected) (figure 1D). Median and p-values are provided in online supplemental table 3. In the CC NAWM, lower NDI and higher ODI values were associated with a higher CC WM LV ($r=-0.585$, p=0.008 and $r=0.440$, p=0.047, respectively). Higher CST NAWM ODI and PTR NAWM ODI were associated with higher CST and PTR WM LV ($r=0.564$, p=0.011; $r=0.514$, p=0.024, respectively).No association was found between the EDSS score and the studied NODDI metrics (p ranging from 0.09 to 0.96).

DISCUSSION

In our cohort of pedMS, we observed that MS-related pathology significantly impacts on tissue integrity in the so-called NAWM. One of the main advantages of NODDI over DTI relies on its ability to disentangle the contributions of axonal/dendritic density and fibres orientation to microscopic changes.[5] The decreased NDI (i.e., loss of neurite integrity) in the investigated tracts seem to indicate that this metric is able to detect axonal damage in a very early MS phase, such as PedMS.[5]

Thus, NODDI could better define the neurobiological substrate underlying brain tissue damage and, possibly, the failure of age-expected development in pedMS.

A positive correlation between NAWM ODI and within tract WM LV was disclosed, reflecting the presence of early fibre disorganisation in the NAWM.[6] We also found a relationship between lower NDI and higher within tract WM LV, supporting the view that axonal damage in the NAWM is primarily related to transected axons degeneration in focal lesions, as previously reported in adult MS.[5] This is further supported by the absence of correlation between NODDI metrics and WM LV in the CST and CP, where a low within tract WM LVs were found.

The lack of correlation between NDI and EDSS score is expected and could indicate that in the very early phases of MS, disability is predominantly driven by inflammation and demyelination. Inflammatory-induced neurodegeneration is expected to subsequently drive the accumulation of physical and cognitive disability later in the disease course, further pointing out the necessity of an early highly effective anti-inflammatory treatment to limit neurodegeneration.

Although the small sample size and the exploratory nature of this study may constitute a limitation of our study, we underline that pedMS is a quite rare disease and that the 19 pedMS patients and the HC here described were studied with the same methodologies and instruments in a single MS Centre, thus ensuring quality and reproducibility of the data.

In summary, NODDI disclosed significant microstructural changes in the NAWM of pedMS. Our findings are particularly relevant since the clinical onset of pedMS is most likely very close to its biological onset, and further provide in vivo evidence supporting the hypothesis that inflammatory-triggered neurodegeneration affects MS brain since the biological onset of the disease.

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