INTRODUCTION and PURPOSE

During the last decade, neurodegeneration has proven to represent a cardinal feature of multiple sclerosis (MS) pathology, starting from the earliest phases of the disease, and the thalamus has been identified as the first gray matter (GM) compartment involved.[1] In pediatric MS patients, thalamic damage and its role in clinical and neuropsychological impairment[2] have been extensively described. However, despite widely recognized, the mechanism leading to thalamic damage still remains unclear, leaving different hypotheses open. Due to its central location and its double interface, on one side with white matter (WM) and on the other side with CSF, the thalamus is likely to be susceptible to both retrograde Wallerian degeneration from WM lesions and CSF immune cytotoxic factor-mediated damage, in addition to intrinsic thalamic pathology.

In this framework, advanced neuroimaging and neuroimaging methods provide us with an increasingly better view of the full extent of pathological processes underlying thalamic damage in patients with MS. A tract-specific pattern of cortico-thalamic neurodegeneration has been described accounting for WM macroscopic and microstructural damage in the thalamus by adopting DTI.[3] Moreover, recent studies have emphasized the existence of an outside-in CSF-mediated pathway underlying a neurodegenerative processes in MS. This last hypothesis has been recently proved by in vivo studies using magnetization transfer imaging[4] in periventricular WM, and in deep GM in MS patients.[5] Nevertheless, to date, only one study in adult MS patients[6] focused on the pathological processes behind thalamic damage. By adopting ultra-high field quantitative imaging, thalamic focal lesions were attributed to CSF-mediated factors and an association was found between thalamic degeneration and WM lesions outside the thalamus. Recently, a novel MRI method based on the ratio of T1/T2-weighted image signal intensities has been introduced, in order to provide an indirect in vivo evidence of myelin content.[7] This method is particularly attractive for MS research and for pediatric studies and it is characterized by high feasibility, adopting two conventional sequences, which are part of many clinical MRI protocols.

Against this background, we combined different MRI techniques to investigate in-vivo the pathological processes behind thalamic damage in pediatric MS patients. In details the aims of this study are:

• To assess thalamic atrophy in pediatric MS patients;
• To explore lesion distribution within the thalamus;
• To investigate microstructural pathology as measured by DTI metrics and T1/T2 ratio in the thalamus and thalamic WM (in order to explore the additional variance in MRI microstructural metrics due to this compartment) as whole and as a function of distance from the ventricles;
• To explore the relationship between the previous abnormalities and WM lesions and cortical pathology as well as their contribution to clinical measures.

MATERIALS AND METHODS

• Subjects: 70 pediatric MS patients and 26 age and sex-matched healthy controls (HC) were enrolled. Patients with acute disseminated encephalomyelitis were excluded according to published operational criteria.[8] None of the patients had a diagnosis of clinically isolated syndrome at the time of study inclusion and all of them had at least two clinical attacks and the formation of new central nervous system lesions on serial MRI.

• Neuroimaging examination:
  - Clinical evaluation;
  - EDSS score rating.

• MRI Acquisition (3.0 T scanner):
  - Dual-echo TSE;
  - 3D T1-weighted fast field-echo scan;
  - Pulsed-gradient SE EPI with SENSE (acceleration factor=2) and diffusion gradients applied in 35 non-collinear directions. Two optimized b factors were used for acquiring diffusion weighted images (b=0 and b=900 s mm-2).

• Conventional MRI analysis:
  - Measurements of T2 hypointensity and T1 hypointensity lesion volumes (LV);
  - Quantification of normalized brain (NBV), WM (NWMV) and GM (NGMV) volumes (SIENAx).

• Quantitative MRI analysis:
  - T1/T2-weighted ratio maps were estimated using an in-house implemented method;
  - Thalamic segmentation (FIRST software);
  - Thalamic segmentation into concentric bands according to geodesic distance from the thalamus/CSF interface;
  - Tract-based spatial statistic to isolate thalamic WM;
  - Assessment of DTI metrics - fractional anisotropy (FA) and mean diffusivity (MD) – and T1/T2 ratio values in whole thalamus, thalamic WM and their concentric bands;
  - Cortical surface reconstruction and mean cortical thickness measurements (FreeSurfer 6.0.0).

Figure 1. Example of thalamic segmentation obtained in a healthy subject is provided. A red-yellow scale shows the different thalamic bands according to the geodesic distance from the CSF.

RESULTS

Table 1. Shows the main demographic and clinical characteristics of the study subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pediatric HC</th>
<th>Pediatric MS patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>26</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>15.15</td>
<td>15.2 (5.5-16.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Median disease duration (range) (years)</td>
<td>-</td>
<td>1.6 (0.4-6.1)</td>
<td></td>
</tr>
<tr>
<td>T2 FLAIR (T2 FLAIR)</td>
<td>-</td>
<td>6.2 (4.7)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 (T1 FLAIR)</td>
<td>-</td>
<td>3.5 (4.8)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 FLAIR (T2 FLAIR)</td>
<td>-</td>
<td>1753 (91)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 FLAIR (T2 FLAIR)</td>
<td>802 (72)</td>
<td>831 (50)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 FLAIR (T2 FLAIR)</td>
<td>802 (51)</td>
<td>829 (50)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 FLAIR (T2 FLAIR)</td>
<td>11.0 (12.4)</td>
<td>10.5 (8.6)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 FLAIR (T2 FLAIR)</td>
<td>11.2 (15.8)</td>
<td>10.6 (9.3)</td>
<td></td>
</tr>
<tr>
<td>FLAIR T1 FLAIR (T2 FLAIR)</td>
<td>2.4 (1.8)</td>
<td>2.3 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Mean lesion volume values [ml] are reported for each thalamic concentric band originating from the CSF-thalamus interface. Abbreviation: CSF-cerebrospinal fluid.

Table 1. Shows the main demographic and clinical characteristics of the study subjects.

Lesions were mainly located in thalamic bands nearest to CSF.

Figure 3 shows MBI quantitative metrics in thalamic concentric bands obtained as function of their geodesic distance from CSF as mean (solid lines) ± standard deviation (dashed lines), for the whole thalamus (upper row) and thalamic WM (lower row).

DISCUSSION

By assessing diffuse microstructural damage, this study confirmed the presence of thalamic damage from the earliest stages of MS.

In conclusion, the hypothesis of an interaction of an immune cytotoxic factor in the CSF mediating thalamic damage, a prominent involvement of the bands nearest to CSF/thalamus interface was found as well as the preferential location of thalamic lesions in these regions. To support this hypothesis, a correlation between thalamic damage in the regions nearest to CSF was found, thus suggesting a common inflammation-mediated pathogenic mechanism.

The involvement of thalamic regions nearest to thalamus/WM interface appeared to be related to Wallerian degeneration phenomena, as suggested by the correlation with T2 lesion volume.

Considering the thalamus as a whole, we found significant differences in thalamic FA (p=0.03) as well as WM FA (p=0.006) and MD (p=0.009).

REFERENCES

3. DeMeo E, et al., Neurology 2014; 83(3); 1,2, 4, 6, 11, 12, 13, 14, 15/11

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