AGE AT DISEASE ONSET INFLUENCES GRAY MATTER AND WHITE MATTER DAMAGE IN ADULT MULTIPLE SCLEROSIS PATIENTS

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INTRODUCTION and PURPOSE

In multiple sclerosis (MS) patients, age of disease onset may influence clinical status (time to reach fixed disability and level of disability) during adulthood [1, 2]. Maturational effects as well as the presence of different pathophysiological mechanisms could contribute to explain different clinical outcomes between patients with pediatric versus adult MS onset.

Previous MRI studies have provided inconclusive results concerning differences of global and regional brain alterations between MS patients with pediatric and adult onset of the disease [3-5]. Disease duration has been suggested to be more related to disease progression and brain damages than age at onset [5-6].

Working question: to what extent do age and disease duration contribute to the clinical profile and brain damage in MS patients?

Aim of the study: to explore the presence and distribution of microstructural alterations within the brain white (WM) and gray matter (GM) in adult MS patients according to their age of disease onset, using advanced voxel-wise methods of MRI analysis.

METHODS

Subjects [Table 1]**:**

- **174 adult MS patients:** 58 pediatric-onset (**PO**; 64% female), 58 adult onset age-matched (**AOA**; 65.5% female), 58 adult-onset disease duration-matched (**AODD**; 67% female);
- **58** right-handed, age- and sex-matched healthy controls (**HC)** (62% female).

Each patients underwent a neurological examination on the day of MRI scan, with rating of the EDSS score [7].

MRI acquisition (3.0 Tesla scanner):

- Axial dual-echo (DE) TSE;
- 3D T1-weighted fast field echo (FFE);
- Diffusion tensor images (DTI).

Image analysis:

- Quantification of T2 lesion volumes (LV) (Jim 6, Xinapse Systems Ltd);
- Segmentation of T1 hypointense lesions on 3D FFE images, previously coregistered to DE scan;
- Measurement of normalized brain (NBV), GM (GMV) and WM (WMV) volumes on 3D FFE images, using the SIENAx software [8], after T1-hypointense lesion refilling.

VBM analysis:

- Pre-processing with Dartel method [9]: spatial normalization, segmentation of the brain in GM and WM matter, Jacobian modulation (Gaussian filter of 8-mm).

TBSS analysis:

- Correction for motion and eddy current distortions [10];
- Estimation of DT, creation of fractional anisotropy (FA) maps;
- Non-linear registration of individual FA images to the FMRIB58-FA atlas;
- Thinning of the resulting mean FA image to create a WM tract "skeleton";
- Projection of individual subject FA maps onto the group skeleton;
- Similar approach for mean diffusivity (MD) maps.

Statistical analysis:

- Demographic, clinical and conventional MRI variables: Mann-Whitney U test and ANOVA models, as appropriate; correlation analysis, using the Spearman rank coefficient;
- VBM: two-sample t-test, including ICV as nuisance variable; multiple regression model for correlations with age at onset (ICV as nuisance variable);
- TBSS: between-group voxel-wise differences of FA and MD using permutation method (5000 permutations, randomized program within FSL), two-sample t tests; correlation analysis with age at onset.

For all measures, the following between-group comparisons were decided *a priori*: 1) HC *vs* PO-MS patients, 2) PO-MS *vs* AOA-MS, 3) PO-MS *vs* AODD-MS and *vice versa*.

Between-group comparisons were adjusted for age or disease duration, as appropriate.

RESULTS

Demographic, clinical and structural MRI findings [Table 1]**:**

-Compared to HC, MS patients had higher T2 and T1 LV, as well as lower NBV, GMV and WMV ($p<0.001$, $p<0.001$ and $p=0.002$, respectively).

-Compared to AODD-MS, PO-MS had lower EDSS ($p=0.006$), lower T1 LV ($p=0.02$) and higher NBV ($p<0.001$), GMV ($p<0.001$) and WMV ($p=0.04$).

Table 1. Main demographic, clinical and structural MRI findings from healthy controls (HC) and patients with MS.

	HC	MS patients	*p*	PO-MS	AOA-MS	AODD-MS	*p*
Mean age [years] (range)	32.9 (19-68)	34.8 (18-67)	n.s.	29.3 (18-61)	29.9 (20-53)	45.3 (24-67)	**<0.001**
Mean age at onset [years] (range)	-	22.8 (9-51)	-	14.7 (9-17)	22.8 (18-40)	30.9 (18-51)	**<0.001**
Mean disease duration [years] (range)	-	12 (1-45)	-	14.3 (2-45)	7.1 (1-21)	14.5 (2-43)	**<0.001**
Median EDSS (range)	-	1.5 (0-8.5)	-	1.5 (0-7.0)	1.5 (0-6.5)	2.5 (1.0-8.5)	**0.003**
Mean T2 LV [ml] (SD)	0.09 (0.5)	9.3 (10.6)	**<0.001**	8.9 (12.5)	8.0 (7.4)	10.9 (11.1)	0.2
Mean T1 LV [ml] (SD)	0.06 (0.3)	6.2 (7.9)	**<0.001**	5.9 (9.4)	5 (4.7)	7.8 (8.7)	0.06
Mean NBV [ml] (SD)	1605 (93)	1517 (114)	**<0.001**	1549 (113)	1538 (108)	1464 (105)	**<0.001**
Mean GMV [ml] (SD)	763 (59)	698 (85)	**<0.001**	720 (92)	719 (72)	656 (75)	**<0.001**
Mean WMV [ml] (SD)	842 (46)	819 (49)	**0.002**	829 (49)	819 (43)	808 (46)	0.1

VBM results [Figure 1]:

-PO-MS *vs* HC: PO-MS patients showed atrophy of the bilateral thalamus, fusiform gyri, middle cingulate cortex, frontal cortex, right caudate nucleus and occipital areas [Figure 1];

-PO-MS *vs* AOA-MS: AOA-MS patients showed a widespread GM atrophy of bilateral fronto-temporo-parieto-occipital areas, as well as of subcortical structures [Figure 1];

-PO-MS *vs* AODD-MS: AODD-MS patients had atrophy of the right fusiform gyrus [Figure 1], whereas PO-MS patients had atrophy of the right superior temporal lobe [Figure 1].

Correlation analysis:

-Significant negative correlation was found between lower GM volume and older age at disease onset in right superior temporal pole and left putamen in PO-MS patients [Figure 2].

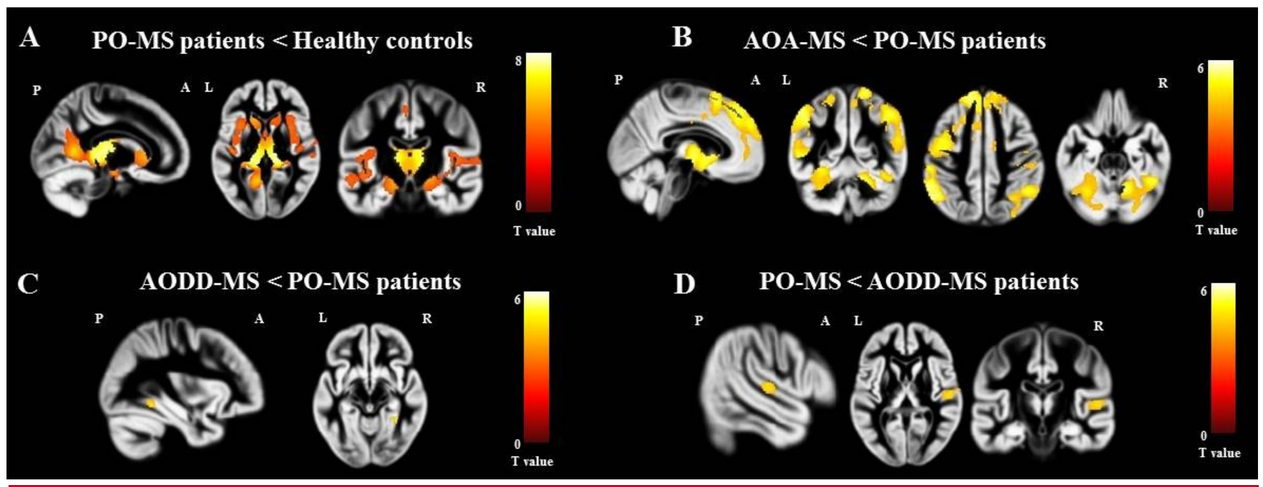

Figure 1 . VBM results. Between-group comparisons of GM volume (A-D; two- sample *t* test, $p<0.001$, uncorrected). Decreased GM volume in PO-MS *vs* HC (A); Decreased GM volume in AOA-MS *vs* PO-MS patients (B) (disease duration-adjusted analysis); Differences of GM volume (C, D) between PO-MS *vs* AODD-MS (age-adjusted analysis).

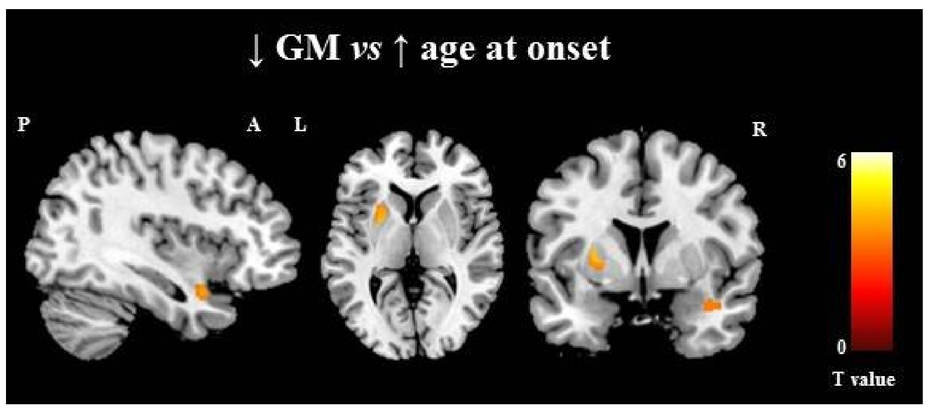

Figure 2 . VBM correlations. Correlation between GM volume and age at onset in PO-MS patients ($p<0.001$, uncorrected).

TBSS results:

- PO-MS *vs* HC: PO-MS patients showed reduced FA and increased MD values in the main supratentorial and infratentorial WM tracts [Figure 3];
- PO-MS *vs* AOA-MS: AOA patients showed reduced FA values in the bilateral internal capsulae, posterior thalamic radiations, corpus callosum, corona radiata and pontine crossing fibers [Figure 3]. No differences of MD values were detected.
- PO-MS *vs* AODD-MS: PO-MS had reduced FA values in the corpus callosum, cingulum, and bilateral portions of internal capsulae, corona radiata, external capsulae and posterior thalamic radiations [Figure 3]. No differences of MD values were detected.
- No correlations between TBSS maps and age at onset were observed in the three MS groups.

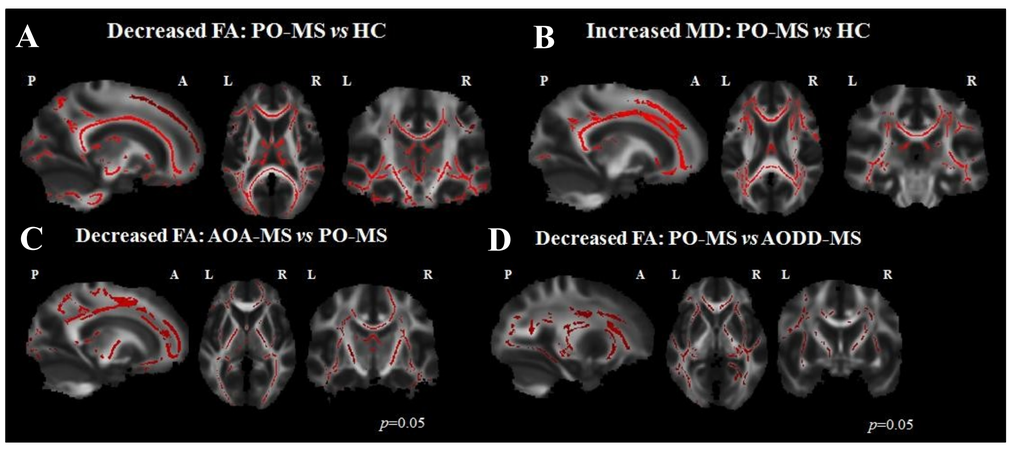

Figure 3. TBSS results. Between group comparisons (A-D; two-sample *t* test). Decreased FA (A) and increased MD (B) in PO-MS patients *vs* HC; decreased FA (C) in AOA-MS *vs* PO-MS patients (disease duration-adjusted analysis); decreased FA (D) in PO-MS *vs* AODD-MS patients (age-adjusted analysis).

CONCLUSIONS

Advanced structural MRI techniques enabled to detect specific patterns of GM and WM alterations in MS patients according to their age of disease onset. Compared to AOA, PO-MS patients had less extensive GM atrophy and less severe NAWM damage, suggesting that neurodegenerative and inflammatory-demyelinating processes could be less pronounced in these patients.

With increasing disease duration, an accelerated NAWM damage seems to occur in PO-MS patients, which suggests an impaired reserve for structural plasticity over the long-term.

In conclusion, this multiparametric MRI study suggests that different pathological processes may occur in MS patients depending on their age of disease onset, contributing to explain their heterogeneous clinical outcome.

REFERENCES

1) Duquette et al., J Pediatr 1987
2) Gorman, Arch Neurol 2009
3) Aliotta et al., Human Brain Mapping 2014
4) Donohue et al., J Neuroimaging 2014
5) Yeh et al., Brain 2009
6) Simone et al., Neurology 2002
7) Kurtke et al. Neurology 1983
8) Smith et al., Radiology, 2011
9) Ashburner, Neuroimage, 2007
10) Rohde et al. Magn Reson Med 2004

DISCLOSURES

L. Vacchi, B. Colombo, M.E. Rodegher, L. Moiola, A. Falini reports no actual or potential conflict of interest.

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