REGIONAL PATTERNS OF BRAIN ATROPHY DEVELOPMENT IN PEDIATRIC AND ADULT MULTIPLE SCLEROSIS PATIENTS: A 3.5 YEAR STUDY

E. De Meo[1,2], E. Pagani[1], B. Colombo[2,], M. Rodegher[2], L. Moiola[2], A.Ghezzi[3] G. Comi[2], A. Falini[4], M. Filippi[1,2,] M.A. Rocca[1,2]

[1]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, [2]Dept. of Neurology, and [4]Dept. of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; [3]MS Center, Ospedale di Gallarate, Gallarate, Italy.

Introduction and purpose

In the last decade, multiple sclerosis (MS) onset during childhood and adolescence has been increasingly recognized. Previous studies aimed at investigating the differences existing between pediatric- and adult-onset patients, identified some distinctive clinical and magnetic resonance imaging (MRI) features [1]. In particular, despite an annualized relapse rate up to 3-fold higher in pediatric onset MS than in adult onset [1], the time to reach irreversible and severe clinical disability was longer in children than in adults [2].

A higher MRI disease burden at presentation and higher disease activity on follow-up scans has been detected in pediatric patients compared to adults at the same disease stage, in addition to a selective infratentorial involvement on the initial brain MRI scan in pediatric-onset MS [3].

We performed a longitudinal MRI study with the following aims:

- **To identify, at voxel level, the differences existing in the regional gray matter (GM) atrophy pattern in pediatric- and adult onset MS, as well as in their changes over time;**
- **To clarify the contribution of the previous abnormalities for clinical outcomes.**

Methods

Subjects: 30 pediatric (pedMS) and 30 adult MS (adMS) patients underwent clinical and MRI evaluation at baseline and after a median follow-up (FU) of 3.2 (range: 2.13-4.25) years. Two groups of HCs were selected for the assessment of GM volume in MS patients at baseline: 1) a group of 26 sex- and age-matched pediatric HC (pedHC), and 2) a group of 30 sex- and age-matched adult HC (adHC) with no previous history of neurological dysfunction and a normal neurological exam.

Neurological examination:

- Clinical evaluation;
- EDSS score rating.

MRI Acquisition (3.0 T scanner):

- Dual-echo TSE;
- 3D T1-weighted fast field-echo scan.

Conventional MRI analysis:

- Measurements of T2 hyperintense and T1 hypointense lesion volumes (LV);
- Quantification of total brain (TBV), white matter (WMV) and GM volumes (GMV) as well as their changes over time performed with SPM 12 software.

Table 1 shows the main demographic and clinical characteristics of the enrolled study subjects at baseline and their changes over time.

	Pediatric HC	Adult HC	Pediatric MS patients	Adult MS patients	p values§
Number of subjects	26	30	30	30	-
Female/male					
Mean age (SD) [years]	-	-	-	-	
Median disease duration (range) [years]	-		-	-	0.26
Median EDSS [range]	-		-	-	0.38
Median EDSS annualized changes [range]	-		- -	- -	<0.001
Mean T2 LV (SD) [ml]	-				0.32
Mean T2 LV annualized change % (range)	-		- -	- -	0.83
Mean T1 LV (SD) [ml]	-				0.27
Mean T1 LV annualized change % (range)			- -	- -	0.02
Mean TBV [ml] (SD)				1105 (117)	0.007
Mean TBV annualized change % (range)	-		- -	- -	<0.001
Mean GMV [ml] (SD)	763 (67)		745 (68)		<0.001
Mean GMV annualized change % (range)	-		- -	- -	<0.001
Mean WMV [ml] (SD)				464 (58)	0.003
Mean WMV annualized change % (range)	-		- -	- -	0.17

* Chi square test.

Abbreviations: HC=Healthy Controls; MS=Multiple Sclerosis; SD=standard deviation; EDSS=Expanded Disability Status Scale; LV=lesion volume; TBV=total brain volume, GMV=gray matter volume; WMV=white matter volume.

MRI analysis (SPM12 software):

- ***VBM (regional GM differences at baseline)*:**
  - Segmentation into GM, WM and CSF;
  - GM and WM segmented images of all subjects were used to produce GM and WM templates and to drive the deformation to the templates;
  - Affine registration between the customized GM template and the SPM GM template in the Montreal Neurological Institute (MNI) space.
- ***TBM (regional pattern of GM atrophy progression)*:**
  - Pairwise longitudinal registration to align the first and second scan of each subject;
  - Volume change quantification;
  - Production from the GM and WM segmented images of GM and WM templates;
  - Normalization to MNI space.

Statistical analysis:

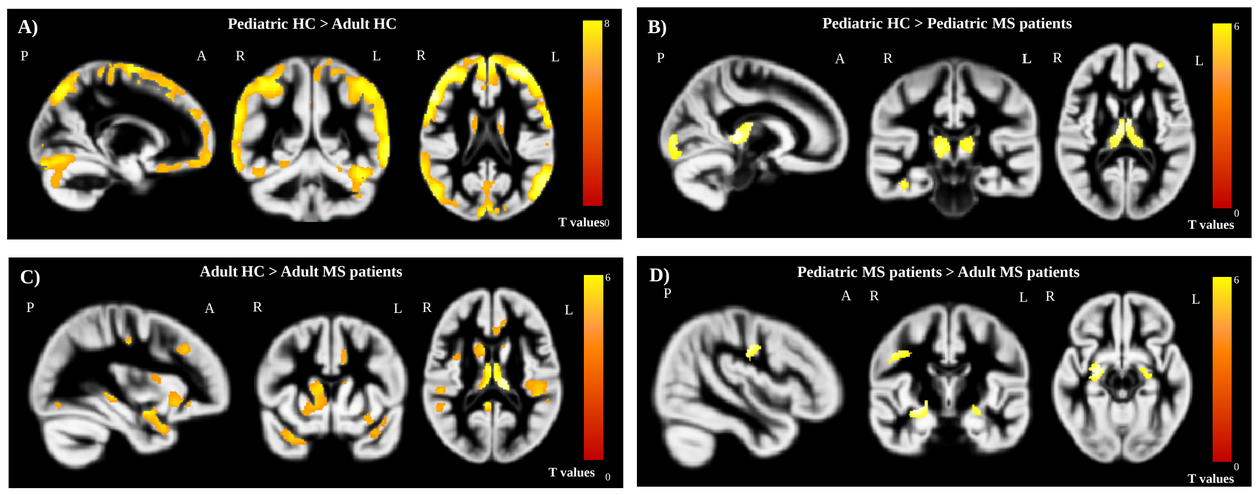
- Full factorial model: GM differences at baseline (adHC *vs* pedHC; adMS *vs* adHC; pedMS *vs* pedHC and adMS *vs* pedMS);
- One sample t test: longitudinal GM changes within group (adMS and pedMS);
- Analysis of covariance (ANCOVA): longitudinal GM volume changes between-groups;
- Multiple regression model: correlations between GM volume changes and clinical and conventional MRI variables.

Results

Regional GM volume differences at baseline (Figure 1):

- Compared to adHC, pedHC showed higher GM volume in both cortical and subcortical regions (A);
- Compared to pedHC, pedMS showed reduced GM volume in bilateral thalamus and inferior forntal gyrus (IFG), left calcarine cortex, supplementary motor area (SMA), parahippocampal, postcentral (PoCG) and inferior temporal (ITG) gyri, superior parietal lobule and right hippocampus and supramarginal gyrus (B);
- Compared to adHC, adMS showed a broader pattern of GM reduction involving frontal, temporal, parietal and occipital lobe and in addition to deep GM structures (C);
- Compared to pedMS, adMS showed reduced GM volume in bilateral hippocampus, left PoCG, middle temporal gyrus (MTG), temporal pole and parahippocampal gyrus, and right precuneus, lingual and middle occipital gyrus (MOG) (D).

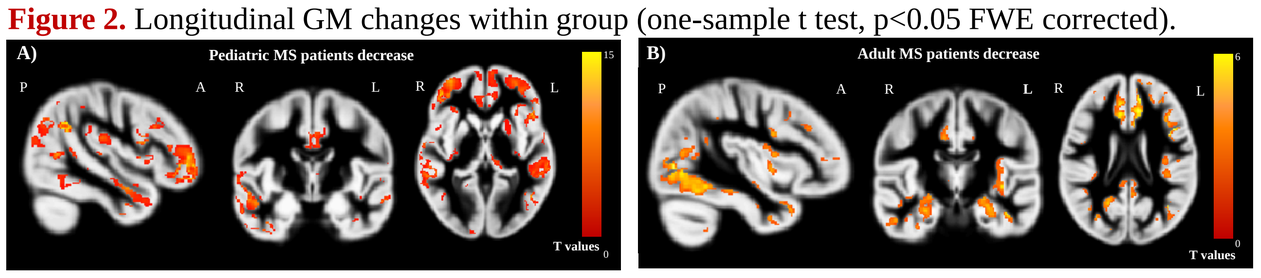
Figure 1. Comparison between pedHC vs adHC, pedHC vs pedMS, adHC vs adMS, pedMS vs adMS (full factorial model, p<0.001).



Regional longitudinal GM changes (Figure 2):

- PedMS (A) and adMS (B) showed a similar pattern of GM atrophy over time.

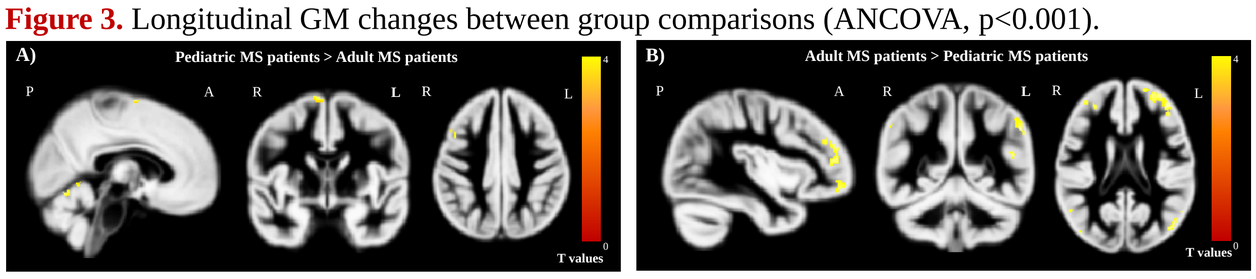
Figure 2. Longitudinal GM changes within group (one-sample t test, p<0.05 FWE corrected).



Between group comparisons of longitudinal GM volume changes (adMS *vs* pedMS) (Figure3):

- PedMS showed less atrophy in bilateral cerebellum and precentral gyrus (PCG), and in left middle frontal gyrus (A);
- PedMS showed more atrophy in several bilateral frontal and temporal regions, middle cingulate cortex and MOG and left precuneus (B).

Figure 3. Longitudinal GM changes between group comparisons (ANCOVA, p<0.001).



Correlation analysis:

- No significant correlations were found between GM atrophy and clinical and conventional MRI variables.

Conclusions

- At baseline, compared to adMS, pedMS patients showed higher GM volume in key brain regions.
- During the FU, pedMS experienced less atrophy progression only in the cerebellum and precentral gyrus, while they experienced more atrophy in anterior frontal and temporal regions.
- These findings let us to suppose that the onset of MS during childhood by interfering with the age-expected brain development, is likely to increase the vulnerability to neurodegenerative processes, especially for brain regions with a maturation during the adolescence.

References

1. Gorman MP et al., Arch Neurol 2009;
2. Simone I.L. et al., Neurology 2002;
3. Waubant E. et al., Arch Neurol 2009;

Disclosures

E. De Meo, E. Pagani, L. Moiola, P. Veggiotti, R. Capra, A. Fiorino, L. Pippolo, M.C. Pera and A. Falini report no conflict of interest; M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis, Teva and Merk Serono and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. A. Ghezzi has served on scientific advisory boards for Merck Serono, Biogen Idec Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Merck Serono, Biogen Idec, Bayer Schering Pharma, and Novartis, Serono Symposia International; served as a consultant for Novartis; and receives research support from Sanofi-Aventis, Biogen Idec, and Merck Serono. M.P. Amato received personal compensation from Merck Serono, Biogen, Bayer Schering, Genzyme, Teva and Novartis for serving on scientific advisory board and for speaking, received financial support for research activites from Merck Serono, Biogen Idec, Bayer Schering, Genzyme, Novartis, Genzyme and Teva. G. Comi has received compensation for consulting services for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche, Almirall, Chugai, Receptos, and Forward Pharma, and compensation for speaking activities for Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, and Roche. M. Filippi is Editor-in-Chief of the *Journal of Neurology*; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Merk-Serono, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Acknowledgments.
Partially supported by grants from Italian Ministry of Health (GR-2009-1529671) and Fondazione Italiana Sclerosi Multipla (FISM2011/R/19, FISM 2012/R/8 and FISM-2016-R-23).