CEREBELLAR 1H-MR SPECTROSCOPY AND DWI STUDY IN PATIENTS WITH FRIEDREICH'S ATAXIA

Laura Ludovica Gramegna[1], Claudia Testa[1], Claudio Bianchini[1], David Neil Manners[1], Rita Rinaldi[2], Giovanni Rizzo[1], Valerio Carelli[3,4], Raffaele Lodi[1], and Caterina Tonon[1]

[1]Functional MR Unit, Department of Biomedical and NeuroMotor Sciences (DiBiNeM), University of Bologna, Bologna, Italy, [2]Unit of Neurology, S.Orsola-Malpighi Hospital, Bologna, Italy, [3]Department of Biomedical and NeuroMotor Sciences (DiBiNeM), University of Bologna, Bologna, Italy, [4]IRCCS Institute of Neurological Science of Bologna, Bologna, Italy

Target audience
Neurologists and neuroradiologists studying differential diagnosis of ereditary ataxia and pathophysiology of Friedreich's ataxia (FRDA).

Purpose
The hereditary ataxias with onset in childhood are a group of heterogeneous disorders. In many of them MRI shows cerebellar atrophy. The most prominent exception to this is Friedreich's ataxia (FRDA), where MRI shows normal cerebellar volume.[1] Most of the neurological symptoms result from neurodegeneration in the dorsal root ganglia and posterior column with loss of large sensory neurons, followed by degeneration in the spinocerebellar and corticospinal tracts of the spinal cord. The dentate nucleus of the cerebellum is also affected, accounting for the cerebellar phenotype. Our aim was to investigate by MRS possible metabolic changes in the cerebellar hemispheres and their relationship with genetic and clinical severity.

Methods
28 FRDA patients were recruited (17 males; age : 29 ±12 y,); all patients were homozygous for a GAA expansion in the FRDA genes. The quantification of disability was performed using the International Cooperative Ataxia Rating Scale (ICARS). MR studies were performed using a 1.5 Tesla GE Signa Horizon LX system equipped with a quadrature birdcage head coil. A volume of interest (VOI) of 2.0 x 2.0 x 1.5 cm^3 was selected in the left cerebellar hemisphere (Figure 1-A). Proton MR spectra were acquired using the PRESS single-voxel localization sequence (PROBE) at TE = 35, with a TR= 4000 ms, averaging 64 FIDs for each acquisition (Figure 1-B). Axial DW images were obtained (slice thickness= 5 mm, inter-slice gap= 1mm) using a single-shot EPI sequence (matrix size = 192x192). Orthogonal x, y and z diffusion-encoding gradients were applied with gradient strengths corresponding to a b-value of 900 s/mm^2. In addition, images without diffusion weighting were acquired, corresponding to b = 0 s/mm^2 and exhibiting T2-contrast. A single-sized region of interest (ROI) of 2.0 x 2.0 x 1.5 cm^3 was placed by an operator with >5 years of experience in neuroimaging and blinded to subjects' diagnoses within the cerebellar white matter area (corresponding to where the MRS single-voxel was placed) and MD values were retrieved excluding the contribution of CSF. Thirty-five healthy volunteers were also included in the study: 15 healthy volunteers (4 male; age 33 ± 8) underwent the ^{1}H-MRS study and 20 healthy volunteers (15 male, age 36 ± 17 y) the DWI study. Metabolites ratios (NAA/Cr, Cho/Cr, mI/Cr) and MD median values corresponding to the VOI in the cerebellar hemisphere were compared between patient and control groups using the Student t-test. For the patients we performed a backward stepwise linear regression to evaluate the dependence between spectroscopy metabolites values that resulted significantly different for patient and control groups and DWI-MD values. The NAA/Cr dependence from demographic and genetic parameter (age, sex, disease duration, therapy intake, GAA expansion) was calculated performing a linear multiple regression with a backward stepwise method. Moreover, in order to check if the possible correlation with GAA1 was age-dependent we corrected both NAA/Cr and ln(NAA/Cr) for age. We didn't include the disease severity score (ICARS score) in this model of linear multiple regression since it was strongly correlated with the disease duration (p=0.001). Thus, we correlated ^{1}H-MRS variables and the ICARS score using a Pearson correlation test. We used a post-hoc test in order to evaluate which subitems of the ICARS score were correlated with ^{1}H-MRS variables. For all analyses, only p values less than 0.05 after Bonferroni correction for multiple comparisons were accepted as statistically significant.

Results
In the cerebellar hemisphere, patients had significant lower NAA/Cr and Cho/Cr ratio in comparison to the controls (Table 1). The MD values calculated in the same VOI showed a significant increase in patients (Table 1). For patients only the NAA/Cr reduction correlated with the increasing of the MD value (p =0.037) (Figure 2). NAA/Cr reduction significantly correlated with disease duration and disease severity (ICARS score). NAA/Cr ratio was found to correlate with all ICARS subscores most significantly with the kinetic one: posture and gait (p = 0.003), kinetic (p=0.001), speech (p=0.005) and oculomotor subscore (p=0.038). We did not find any correlation between NAA/Cr and GAA1.
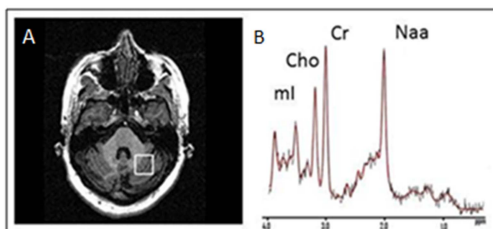

Figure 1.

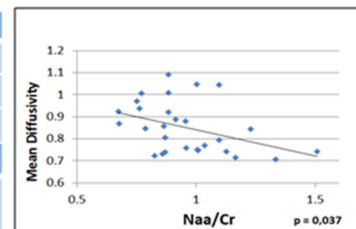| Metabolite ratios	Controls (=15)	FRDA	P
NAA/Cr	1.28±0.19	0.96±0.19	<0.001
Cho/Cr	0.28±0.04	0.24±0.03	0.004
mI/Cr	0.71±0.11	0.67±0.14	0.436
DWI parameters	Controls (=20)	FRDA	P
Mean Diffusivity (x10^{-3} mm^2/s)	0.59±0.08	0.85±0,11	<0.001

Table 1.

Figure 2.

Discussion
Microstructural changes have been detected by DWI in the cerebellar hemispheres of FRDA patients.[2] As we found in FRDA patients a correlation between MD increase and NAA/Cr decrease, we can speculate that neuronal loss/damage is responsible for higher MD values. The strong correlation between NAA/Cr levels and the severity of the clinical variables, in the absence of correlation between NAA/Cr and GAA1 expansion, suggests that in FRDA the neuronal loss/damage is a post-natal progressive process.

Conclusion
Even in absence of conventional MRI abnormalities, ^{1}H-MRS demonstrated subtle metabolic alterations in the cerebellum of FRDA patients. Metabolic abnormalities correlated with diffusion parameters and clinical scores. Biomarkers derived from ^{1}H-MRS can be used to monitor disease progression and to evaluate the effect of therapy intervention in clinical trials.

References
[1]Wolf NI, Koenig M. Progressive cerebellar atrophy: hereditary ataxias and disorders with spinocerebellar degeneration. Handb Clin Neurol. 2013;113:1869-78.
[2]Rizzo G, Tonon C, Valentino ML, Manners D, Fortuna F, Gellera C, Pini A, Ghezzo A, Baruzzi A, Testa C, Malucelli E, Barbiroli B, Carelli V, Lodi R. Brain diffusion-weighted imaging in Friedreich's ataxia. Mov Disord. 2011 Mar;26(4):705-12.