Characterization of Cerebellar Metabolic Alterations in Ataxia with Oculomotor Apraxia (AOA2)

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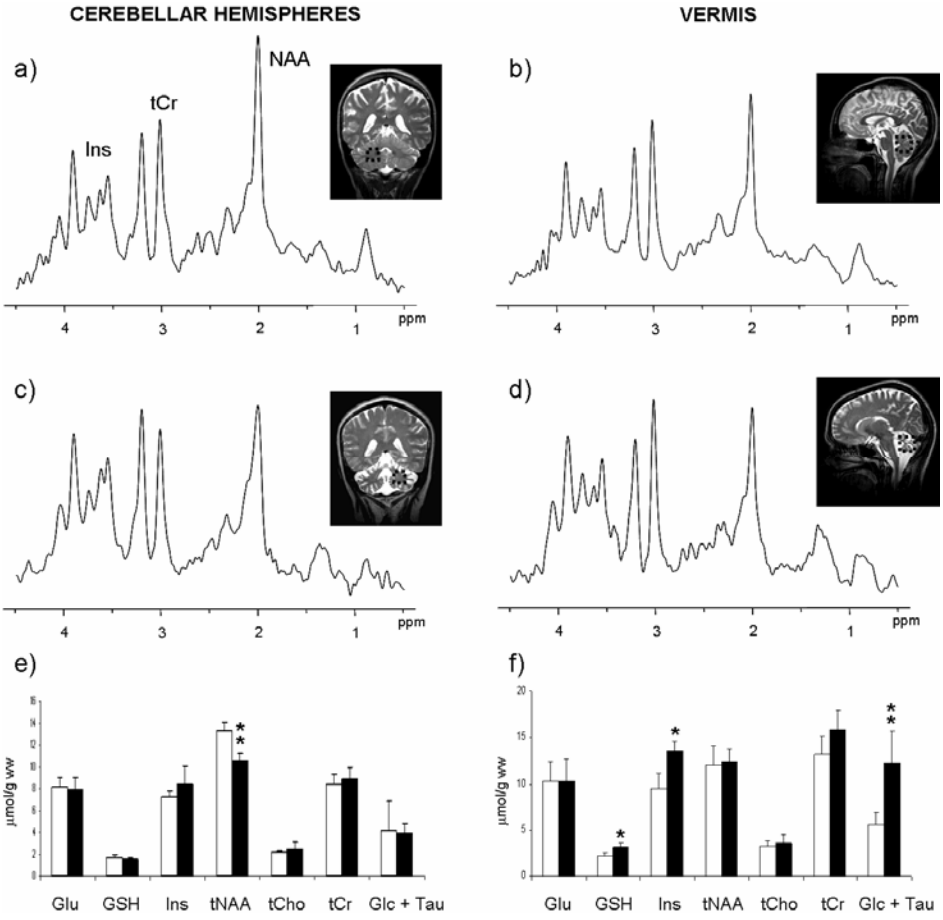
Objective. Ataxia with oculomotor apraxia type 2 (AOA2) is a neurodegenerative disorder which has been recently described as the second most frequent autosomal recessive cerebellar ataxia after Friedreich's ataxia (1). The gene involved in this disease has only been recently described (1,2), and the metabolic alterations involved in this disease have not been elucidated yet. Here, we report for the first time the ^{1}H MRS neurochemical profile of three regions in the brain of patients with AOA2, namely the vermis, the cerebellar hemispheres and the pons. The cerebellar structures were selected based on prior histopathological findings (2). Spectroscopic data were acquired in the pons for comparison with other forms of cerebellar ataxias, which display metabolic alterations in this area (3,4).



Methods. Eleven healthy volunteers (6 F/5 M, average age ± SD, 27 ± 6 years) and 3 patients with AOA2 (2 F/1 M, average age ± SD, 32±8 years) participated in this study. Experiments were conducted at a 4T/ 90 cm wide bore magnet (Oxford) equipped with a Varian console. A TEM volume coil was used for rf transmission and reception. A STEAM sequence (TE = 5 ms, TR = 4.5 s) with outer volume suppression was used for ^{1}H localized spectroscopy (5) in three areas of the brain (cerebellar hemisphere: VOI = 4.9 ml, vermis: VOI = 6.3 ml, pons: VOI = 4.1 ml). Spectra were analyzed using LC Model with water as an internal reference for absolute quantification of the metabolites. Metabolite concentrations were corrected for the amount of cerebrospinal fluid (CSF) in each voxel, assessed by the biexponential decay of the localized water signal at a series of TE values.

Figure. *Spectra from a control participant (a, b) and a patient (c, d) acquired in the cerebellar hemispheres (a, c) and the vermis (b, d). e, f, Metabolite levels (mean ± SD) of controls (open bars, n= 11) and patients (closed bars, n=3) in the cerebellar hemispheres (e) and in the vermis (f). *p < 0.005, **p < 0.001.*

Results. Despite the small number of patients, significant metabolic alterations were detected. In the pons, no significant alterations in metabolite concentrations were observed. The vermis of patients with AOA2 exhibited higher concentrations of glutathione (GSH, + 43 %, p = 0.0037), *myo*-inositol (Ins, + 43 %, p = 0.0014) and glucose + taurine (Glc+Tau, + 119 %, p = 0.0002) compared to controls. In the cerebellar hemisphere, N-acetylaspartate (NAA) was significantly decreased compared to controls (- 21 %, p = 0.0008). The significant cerebellar atrophy also lead to a higher CSF content in patients (patients vs. control: vermis, 59 ± 10 % vs. 10 ± 3 %, p < 0.0001, cerebellar hemisphere, 11 ± 4 % vs. 1 ± 1 %, p < 0.0001).

Discussion. The pons appears to be spared in this disease. High level of *myo*-inositol is in agreement with the mild fibrous gliosis which has been described to be more pronounced in the vermis than in the hemispheres in post-mortem studies (2). In the remaining vermis tissue, the majority of the neurons appear to be viable, as indicated by the preserved levels of NAA and glutamate. Surprisingly, glutathione is elevated in this region and may reflect an altered oxidative status. Neuraxonal loss in the cerebellar hemispheres is likely to be responsible for the lower NAA level observed in this region. To our knowledge, this is the first report about neurochemical alterations in the brains of patients with AOA2.

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