Micro-structural cerebral damage in hereditary spastic paraplegia caused by SPG4 mutations (SPG4-HSP)

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Abstract
Hereditary spastic paraplegia caused by SPG4 mutations is the most frequent form of the disease and classically considered a spinal disorder. Little is known about encephalic damage in SPG4-HSP. This study was then carried out to identify micro-structural white matter (WM) damage in SPG4-HSP patients. We selected 11 patients with molecular confirmation of the disease and 23 healthy controls matched by age and gender. These subjects underwent magnetic resonance imaging (MRI) on a 3T Achieva-Intera PHILLIPS scan. Diffusion tensor images (DTI) were obtained using a specific Spin echo DTI sequence. Fractional anisotropy (FA) and axial (AD), radial (RD) and mean diffusivity (MD) maps were then created using the FMRIB tool on FSL v.4.1.4 software. These maps were used to search for damage in patients when compared to controls. This comparison was performed using TBSS, a algorithm in FSL v.4.1.4. A two sample t-test (p-value <0.05) was used to identify differences between the two groups. TBSS analysis revealed micro-structural impairment in patients, with FA reduction and AD and RD increase in corticospinal tracts, posterior cingulate gyri and the splenium of the corpus callosum. We conclude that SPG4-HSP patients present micro-structural damage in motor and non-motor areas of the brain. Diffusion tensor imaging, spastic paraplegia, Neurogenetics.

Introduction
HSPs are a group of neurodegenerative disorders characterized by progressive spasticity and weakness in the lower limbs (1). They can be inherited as autosomal recessive, autosomal dominant (AD) or X-linked diseases (2). Mutations in SPG4 gene are responsible for most cases of AD-HSP (3). Nevertheless, few studies evaluated the specific CNS areas affected in SPG4-HSP. Our objective was to investigate micro-structural WM damage in these patients. DTI is a sensitive method to identify damage to WM tracts even before volumetric and macrostructural alterations appear (4).

Results and Discussion
Mean age of patients was 46.0 ± 15.0 years (5 women). TBSS analysis revealed areas of WM damage in patients when compared to controls. There was FA reduction combined with AD and RD increase in the corticospinal tracts, posterior cingulate gyri and the splenium of the corpus callosum. AD is an important marker for axonal damage, while RD is for demyelination. Our findings suggest that both processes are involved in the disease, but axonal impairment predominates. SPG4-HSP patients present micro-structural damage in motor and non-motor WM tracts, specially associated with axonal degeneration. Further studies are needed to evaluate clinical relevance of these findings.

Conclusions

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