**Dystonia in Machado-Joseph Disease: Clinical Profile, Therapy and Anatomical Basis**

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**Introduction:** Machado-Joseph disease (MJD/SCA3) is the most frequent spinocerebellar ataxia and has remarkable clinical heterogeneity [1]. In this sense, dystonia is frequent in (MJD/SCA3), but several important aspects are not yet defined, such as the detailed clinical profile, response to treatment and anatomical substrate.

**Materials and Methods:** We screened 75 consecutive patients and identified those with dystonia. The Burke-Marsden-Fahn Dystonia Rating Scale was employed to quantify dystonia severity. Patients with dystonia received levodopa 600 mg/day for 2 months and were videotaped before and after treatment. A blinded evaluator rated dystonia in the videos. Patients with disabling dystonia who failed to respond to levodopa treatment received botulinum toxin. Finally, volumetric T1 and diffusion tensor imaging sequences were obtained in the dystonic group using a 3T-MRI scanner (Philips Achieva) to identify areas of gray and white matter that were selectively damaged.

**Results:** There were 21 patients with dystonia (28%): 9 classified as generalized and 12 as focal/segmental. Patients with dystonia had earlier onset and larger (CAG) expansions (28.9 ± 11.7 vs 40.6 ± 11.4; p < 0.001 and 75 vs 70; p < 0.001, respectively). Although group analyses failed to show benefit on levodopa (p = 0.07), some patients had objective improvement. In addition, ten patients received botulinum toxin resulting in a significant change in dystonia scores after 4 weeks (p = 0.03). Patients with dystonia had atrophy at pre- and paracentral cortices; whereas, non-dystonic patients had occipital atrophy. Basal ganglia volume was reduced in both groups, but atrophy at the thalami, cerebellar white matter and ventral diencephali was disproportionately higher in the dystonic group. We found similar white matter abnormalities in both groups.

**Discussion:** We have shown that dystonia is frequent in MJD/SCA3, often disabling and clinically heterogeneous. However, it might respond to levodopa and to botulinum toxin injections. Dystonic patients showed a pattern of cerebral damage different than patients without dystonia. These results indicate that dystonia in MJD/SCA3 is associated with structural abnormalities in the basal ganglia and cerebral cortex. In addition, disproportionate thalamic atrophy in dystonic patients is in agreement with a previous study from our group that employed manual volumetry [2]. This is a reasonable finding since the thalamus is involved both with motor output control and sensory-motor integration, which are two important aspects in the pathogenesis of dystonia. Furthermore, it is well established that focal thalamic lesions might lead to delayed contralateral dystonia in at least 30% of cases [3]. A novel finding in this study was the presence of cortical atrophy around the central sulcus in dystonic subjects. This is in line with recent neuroimaging studies that highlighted abnormal structure and function of sensory-motor cortices in different forms of primary dystonia [4]

**Conclusion:** Dystonia in Machado-Joseph disease is frequent and often disabling, but may respond to levodopa. It is associated predominantly with structural abnormalities around the motor cortices and in the thalami.

**References:** [1] D’Abreu A et al., Parkinsonism Relat Disord 16: 2-7, 2010; [2] D’Abreu A et al., J. Neuroimaging 21: e91-e93, 2011; [3] Lehericy S et al., Neurology 57: 1055-1066, 2001; [4] Piccinin CC et al., Front. Neurol. 8(5): 283, 2015.