Sensitivity of advanced MR imaging to progression over 6 months in early spinocerebellar ataxia

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**ABSTRACT:**

**Background:** Gene silencing therapies are in the pipeline for common spinocerebellar ataxias (SCAs) (Ashizawa et al, 2018), however clinical outcomes are not sensitive to early disease progression, preventing trials at a stage when such therapeutics will be most effective (Piccinin et al, 2020). READISCA, a trans-Atlantic consortium (Chandrasekaran et al, 2023), investigated whether advanced multimodal MRI detects pathology progression over 6 months in preataxic and early ataxic carriers of SCA mutations.

**Methods:** In this prospective longitudinal study 44 participants (n(SCA1)=10, n(SCA3)=25, n(control)=9; including 44% preataxic gene carriers) were scanned at 3T at baseline and after a median [IQR] follow-up of 6.2 [5.9-6.7] months. Structural, diffusion MRI and MR spectroscopy data were analyzed blinded to diagnosis. Ataxia severity was assessed using the scale for assessment and rating of ataxia (SARA). Annual change of MR measures and SARA was compared between groups using nonparametric testing.

**Results:** Rate of change in microstructural integrity (decrease in fractional anisotropy (FA), increase in diffusivities) in the middle cerebellar peduncle (MCP), corona radiata and superior longitudinal fasciculus significantly differed in SCAs from controls with high effect sizes and moderate-high responsiveness, e.g., FA of MCP median [IQR], controls 4.57e-03 [1.69e-03;8.28e-03]; SCA1 -8.4e-03 [-1.15e-02;-3.72e-03], P=.002, Cohen’s d=1.7, SRM=-0.9; SCA3 -2.84e-03 [-1.61e-02;7.17e-04], P=.002, d=1.3, SRM=-0.6. SARA scores did not change, and their rate of change did not differ between groups.

**Conclusions:** Diffusion MRI is sensitive to disease progression in a trial-relevant follow-up period at very early stage SCA1 and SCA3, allowing a ~5-fold reduction in estimated sample sizes from that based on clinical endpoints for interventional trials of 6-month duration using imaging.

**REFERENCES**

Ashizawa T, Oz G, Paulson HL. (2018). Spinocerebellar ataxias: prospects and challenges for therapy development. Nat Rev Neurol;14(10):590-605.

Chandrasekaran J, Petit E, Park YW, et al. (2023). Clinically Meaningful Magnetic Resonance Endpoints Sensitive to Preataxic Spinocerebellar Ataxia Types 1 and 3. Ann Neurol;93(4):686-701.

Piccinin CC, Rezende TJR, de Paiva JLR, et al. (2020). A 5-Year Longitudinal Clinical and Magnetic Resonance Imaging Study in Spinocerebellar Ataxia Type 3. Mov Disord;35(9):1679-84.

Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. (2006). Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology;66(11):1717-20.