**Sensory and corticospinal signs before ataxia onset in SCA1 and SCA3: the READISCA study**

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Background and Objective: READISCA is a prospective, longitudinal observational study of spinocerebellar ataxias type 1 and 3 to provide essential markers for therapeutic interventions. We assessed clinical outcome assessment, imaging and blood biomarker scores during preataxic and early ataxic stages in SCA1 or SCA3 mutation carriers and matched controls.

Methods: We enrolled 200 participants from 18 US and two European ataxia referral centers. READISCA uses a large battery of clinical, cognitive, quantitative motor, neuropsychological measures and plasma neurofilament light chain (NfL) measurements. We calculated estimated time from onset as the difference between the age at the baseline visit and the predicted age at ataxia onset.

Results: There were 45 carriers of a pathological *ATXN1* expansion including 31 ataxic subjects (median SARA: 9 [7;10]) and 14 preataxic individuals (1 [0;2]); 116 carriers of a pathological *ATXN3* expansion, including 80 ataxic subjects (7 [6;9]) and 36 preataxic individuals (1 [0;2]). In addition, we enrolled 39 controls. Plasma NfL levels were significantly higher in preataxic individuals than controls, despite similar mean age (controls: 5.7 pg/mL, SCA1: 18.0 pg/mL (P <0.0001), SCA3: 19.8 pg/mL (P<0.0001). Preataxic individuals differed from controls by significantly more upper motor signs (SCA1 P=0.0003, SCA3 P=0.003) and by the presence of sensor impairment and diplopia in SCA3 (P=0.0448, and 0.0445 respectively). Ataxic participants were worse than preataxic individuals for most of the clinical outcomes.

Discussion and Conclusion: READISCA showed the feasibility of harmonized data acquisition in a multi-national network of 200 baseline SCA1, SCA3 and control individuals. NfL alterations, early sensory ataxia and corticospinal signs were quantifiable between preataxic participants and controls. Ataxic patients differed in many parameters from controls and preataxic individuals, with a graded increase of abnormal measures from control to preataxic to ataxic cohorts.

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