32 Conversion of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 to manifest ataxia in the longitudinal RISCA study

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Background: Spinocerebellar ataxias (SCAs) are fully penetrant autosomal dominantly inherited progressive ataxia disorders. At risk individuals for SCAs provide a unique research opportunity to prospectively study the premanifest disease phase.

Methods: The prospective study of individuals at risk for spinocerebellar ataxia type 1,2,3 and 6 (RISCA) is a multinational, longitudinal observational study.[1] 302 non-ataxic (SARA score <3) adult individuals that descended from an SCA patient (offspring and sibs) were included. Conversion to ataxia was defined by a SARA score ≥3. We did anonymous genetic testing from all study participants. Follow-up assessments were done in 2-year intervals. Assessment included clinical scales, questionnaires, and performance-based coordination tests. MRI was performed in a subgroup of participants. In this analysis, we included 252 individuals who had at least one follow-up.

Findings. Between Sept 13, 2008 and October 28, 2015, 302 participants were enrolled. We analysed data for 252 participants with at least one follow-up visit. 26 (52%) SCA1, 22 (59%) SCA2, 11 (42%) SCA3, and 2 (13%) SCA6 mutation carriers converted to ataxia. Factors predicting conversion were age (HR 1.13, 95% CI 1.03-1.24), CAG repeat length (1.25, 1.11-1.41), and confidence rating (1.72, 1.23-2.41) for SCA1; age (1.08, 1.02-1.14) and CAG repeat length (1.65, 1.27-2.13) for SCA2; and age (1.27, 1.09-1.50), confidence rating (2.60, 1.23-5.47), and double vision (14.83, 2.15-102.44) for SCA3. From the time of inclusion, SARA scores of SCA1, SCA2, and SCA3 mutation carriers increased in a linear way, whereas they remained stable in non-carriers. On a time scale defined by the predicted time of ataxia onset, SARA progression in SCA1, SCA2, and SCA3 mutation carriers was

non-linear. SARA increased only slightly before, but strongly after onset of ataxia. Annual MRI volume loss of cerebellar and brainstem regions was larger in SCA1 and SCA2 mutation carriers than in non-carriers.

Discussion: This study provides quantitative information on the conversion of individuals at risk to manifest ataxia. In addition, the study provides data for the development of clinical and patient-related outcome measures as well as of MRI volumes in these individuals.

[1] Jacobi H, Reetz K, du Montcel ST et al.. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. Lancet Neurol. 2013 Jul;12(7):650-8.