8 Natural history of polymerase gamma related ataxia

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Objective: To determine the course of disease and progression in POLG-related ataxia.

Methods: In a prospective natural history study, we assessed a cohort of 24 adult ataxia patients with biallelic POLG mutations for (i) severity of cerebellar dysfunction using the Scale for the Assessment and Rating of Ataxia (SARA), (ii) presence of non-ataxia signs using the Inventory of Non-Ataxia Symptoms (INAS), (iii) grey and white matter changes in brain MRI, and (iv) findings in nerve conduction studies.

Results: Longitudinal assessment included follow-up visits up to 11.6 years (mean 4.7±3.5). Severity of disease showed a strong linear progression of 1.40 SARA points/year ($R2=0.41$, $p<0.001$). The INAS revealed an increase in INAS count of 0.31 points/year. External ophthalmoplegia, brainstem oculomotor signs, areflexia and sensory deficits were the most common non-ataxic features. On MRI cerebellar atrophy was mostly mild and with no relevant changes for at least 4 years of follow-up. T2 signal alterations affected most frequently cerebellar white matter, middle cerebellar peduncles, thalamus, brainstem, and occipital and frontal white matter. Within four years, progress in lesion load was only observed in pontine and olivary lesions or in the context of repeated epileptic seizures. Nerve conduction studies revealed axonal sensory peripheral neuropathy in all patients with mild motor nerve involvement in 58% of cases. Exploratory sample size calculation implied 58 patients per arm as sufficient to detect a reduction of progression by 50% in hypothetical interventions.

Conclusion: The results recommend SARA as a primary outcome measure for future interventional trials in POLG-related ataxia.