Hereditary Spastic Paraplegia SPG5: Clinical course and therapeutic strategies

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Hereditary Spastic Paraplegia (HSP) SPG5 is caused by mutations in the oxysterol hydroxylase gene CYP7B1. We have collected 22 genetically confirmed SPG5 cases from 19 families. Clinically, SPG5 is characterized by spastic paraplegia accompanied by moderate or severe dorsal column sensory deficits leading to afferent ataxia in the majority of cases. Neurophysiological testing demonstrates widespread, in part subclinical, central involvement while the peripheral nervous system is spared. The MRI is typically normal in early disease stages while progressive cerebellar and supratentorial atrophy and mild T2 hyperintensities in the supratentorial deep white matter evolve at later disease stages. Using the Spastic Paraplegia Rating Scale (SPRS), a validated measure for disease severity in HSP (Schüle et al. Neurology 2006), we establish the natural progression rate of SPG5 in this cohort, an indispensable prerequisite to plan and perform clinical studies. As shown previously in a smaller cohort (Schüle et al. J Lipid Res 2010), oxysterol levels in serum and CSF of SPG5 cases are markedly elevated compared to controls and cause metabolic breakdown and decreased viability in neuronal cell models. We therefore hypothesize that elevated oxysterol levels directly contribute to neuronal damage in SPG5 and that lowering of pathologically elevated oxysterol levels might stop or slow down progression. In a proof-of-principle pilot study we demonstrate in three patients, that treatment of SPG5 patients with a drug modifying cholesterol metabolism can decrease oxysterol levels in CSF and serum by about one third. A randomized controlled trial is in preparation to study this effect further.