Promising treatment found for SPG5 HSP

Atorvastatin reduces toxic fatty compounds in the brain

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This multicentre study has demonstrated the effectiveness of Atorvastatin in reducing toxic levels of oxysterols in the neurons that result from an enzyme deficiency associated with the gene mutation. The study also correlated disease severity and progression with oxysterol concentrations. As expected with a short-term trial (9 weeks) there were no effects on clinical outcome measures.

Abstract

Spastic paraplegia type 5 (SPG5) is a rare subtype of hereditary spastic paraplegia, a highly heterogeneous group of neurodegenerative disorders defined by progressive neurodegeneration of the corticospinal tract motor neurons. SPG5 is caused by recessive mutations in the gene CYP7B1 encoding oxysterol-7α-hydroxylase. This enzyme is involved in the degradation of cholesterol into primary bile acids. CYP7B1 deficiency has been shown to lead to accumulation of neurotoxic oxysterols.

In this multicentre study, we have performed detailed clinical and biochemical analysis in 34 genetically confirmed SPG5 cases from 28 families, studied dose-dependent neurotoxicity of oxysterols in human cortical neurons and performed a randomized placebo-controlled double blind interventional trial targeting oxysterol accumulation in serum of SPG5 patients.

Clinically, SPG5 manifested in childhood or adolescence (median 13 years). Gait ataxia was a common feature. SPG5 patients lost the ability to walk independently after a median disease duration of 23 years and became wheelchair dependent after a median 33 years. The overall cross-sectional progression rate of 0.56 points on the Spastic Paraplegia Rating Scale per year was slightly lower than the longitudinal progression rate of 0.80 points per year.

Biochemically, marked accumulation of CYP7B1 substrates including 27-hydroxycholesterol was confirmed in serum (n = 19) and cerebrospinal fluid (n = 17) of SPG5 patients. Moreover, 27-hydroxycholesterol levels in serum correlated with disease severity and disease duration.

Oxysterols were found to impair metabolic activity and viability of human cortical neurons at concentrations found in SPG5 patients, indicating that elevated levels of oxysterols might be key pathogenic factors in SPG5.

We thus performed a randomized placebo-controlled trial (EudraCT 2015-000978-35) with atorvastatin 40 mg/day for 9 weeks in 14 SPG5 patients with 27-hydroxycholesterol levels in serum as the primary outcome measure. Atorvastatin, but not placebo, reduced serum 27-hydroxycholesterol from 853 ng/ml [interquartile range (IQR) 683-1113] to 641 (IQR 507-694) (-31.5%, P = 0.001, Mann-Whitney U-test). Similarly, 25-hydroxycholesterol levels in serum were reduced. In cerebrospinal fluid 27-hydroxycholesterol was reduced by 8.4% but this did not significantly differ from placebo. As expected, no effects were seen on clinical outcome parameters in this short-term trial.

In this study, we define the mutational and phenotypic spectrum of SPG5, examine the correlation of disease severity and progression with oxysterol concentrations, and demonstrate in a randomized controlled trial that atorvastatin treatment can effectively lower 27-hydroxycholesterol levels in serum of SPG5 patients. We thus demonstrate the first causal treatment strategy in hereditary spastic paraplegia.

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