

P15. LOCOMOTION ALTERATIONS IN BDNF ZEBRAFISH MUTANTS: FIRST INSIGHTS INTO ITS GENETIC PATHWAY

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Background: GDP mannose pyrophosphorylase B (GMPPB) deficiency is one of several dystroglycanopathies, a heterogeneous group of neuromuscular disorders characterized by progressive myopathy, brain and eye abnormalities, and intellectual disability. GMPPB catalyzes the formation of GDP-mannose, required for mannosylation and glycosylation of alpha-dystroglycan (ADG).

Patient and methods: In a patient with GMPPB deficiency due to GMPPB gene mutations (p.Q234X/p.T153I), presenting with hypotonia, elevated serum creatine kinase, psychomotor delay, seizures, and bilateral cataracts, we found a profound deficiency of the lysosomal acid alpha-glucosidase (GAA).

Results: GAA activity in fibroblasts was 2.61 nmol/mg prot/h (NV 64.4 ± 22.9). The molecular analysis of the GAA gene was negative. A western blot analysis showed impaired processing of GAA in fibroblasts. GAA was mostly detectable as the 110 kDa precursor isoform, with near-complete deficiency of the mature 70 and 76 kDa peptides. Conversely, exogenous recombinant human GAA (Myozyme) was normally internalized and processed into the mature GAA. Moreover, PAS staining showed glycogen accumulation, which disappeared in cells treated with Myozyme. In addition, we found reduced activities of beta-galactosidase, alpha-galactosidase, alpha-mannosidase, beta-glucosidase and alpha-fucosidase, suggesting an impairment of multiple lysosomal enzymes.

Conclusions: Our results suggest aberrant processing of endogenous GAA in our patient's fibroblasts, possibly due to defective glycosylation and mannose-6-phosphate generation. We speculate that defective GMPPB function impacts not only on ADG, but also on glycosylation of other glycoproteins, including lysosomal enzymes. It is possible that secondary GAA deficiency contributes to the pathophysiology of muscle disease in GMPPB deficiency.

