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Beneficial prenatal levodopa therapy in autosomal recessive GTP cyclohydroxylase I deficiency

N. Brüggemann, J. Spiegler, Y. Hellenbroich, T. Opladen, S.A. Schneider, R. Boor, U. Stephani, G. Gillessen-Kaesbach, J. Sperner, C. Klein (Lübeck, Germany)

Objective: To report the first prenatal dopaminergic replacement therapy in autosomal recessive GTP cyclohydroxylase (AR GTPCH) deficiency without hyperphenylalaninemia.

Background: AR GTPCH deficiency without hyperphenylalaninemia is a rare form of dopa-responsive dystonia presenting with a complex phenotype, distinct clinical features and an infantile onset in most cases. Prenatal diagnosis and initiation of dopaminergic replacement therapy have not been described so far.

Methods: Mutation analysis of the GCH1 gene, longitudinal case descriptions.

Results: The figure shows the pedigree of a consanguineous family with two siblings (IV.1 and IV.2, filled symbols) carrying homozygous mutations in the GTP cyclohydroxylase 1 (GCH1) gene.[figure1]Confirmed asymptomatic carriers of a single GCH1 mutation are marked by a dot.
In fibroblasts of IV.1, the GTPCH activity was considerably reduced with values between 17 and 31%. He presented with typical features of AR GTPCH deficiency including truncal dystonia, severe spastic tetraparesis, lack of head control as well as intermittent opisthotonus and oculogyric crises. Levodopa treatment was initiated at the age of 10 months and resulted in a distinct motor improvement including a complete resolution of spasticity. Re-occurrence of oculogyric crises, spasticity and abnormal head position were good clinical predictors for the necessity to increase the levodopa dosage. Mental development was, however, moderately delayed despite levodopa treatment.
In the younger sibling IV.2, prenatal replacement therapy was initiated after a prenatal diagnosis of AR GTPCH deficiency was made. At the age of 17 months, both motor and mental development was normal for his age.

Conclusions: Reduced dopaminergic neurotransmission in the developing brain of children may result in an impairment of motor and mental maturation. This report highlights the importance of an early diagnosis, including prenatal diagnosis, of complex dopa-responsive extrapyramidal syndromes.