Title: Cerebral Folate Deficiency - Newborn-Screening makes sense

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Folates are essential cofactors for one-carbon methyl transfer reactions involving synthesis of amino acids, neurotransmitters, DNA and regulating gene expression. Humans need to take up about 0.5 mg of dietary folate per day which is transported from the gut into the vascular system by the proton-coupled intestinal transporter (PCFT). From the liver, the main active metabolite 5-methyl-tetrahydrofolate (5MTHF) is delivered to other organs including the brain using an active 5MTHF transport across the choroid plexus into the CSF. Deficiency of 5MTHF transport across the choroid plexus is caused by pathogenic mutations in the *FOLR1* gene coding for folate receptor alpha (FRα) and is associated with cerebral folate deficiency (CFD) leading to hypomyelination and brain atrophy. Pathogenic mutations in the *PCFT* gene cause hereditary folate malabsorption that manifest with systemic folate deficiency in early infancy. Several other disorders of folate metabolism are known to be associated with CFD.

We have analyzed clinical and biochemical data as well as quantitative MR-imaging from patients carrying pathogenic mutations in the *FOLR1* or *PCFT* gene over more than 10 years of folate treatment. Therapy was mainly started and continued with folinic acid that is readily metabolized to 5MTHF. CSF concentration of 5MTHF quickly normalized after the onset of folinic acid treatment in FRα-deficient patients but poorly correlated with the clinical status. However, the restoration of myelination that was monitored by MR imaging correlated with gradual clinical improvement under therapy. The age at therapy onset was crucial for the clinical prognosis and became particularly evident by families with several affected children. Presymptomatic oral folinic acid treatment resulted in complete normal development. Therapy onset at the very beginning of symptoms, usually at two years of age, required additional intravenous folinic acid to restore myelination and rescue most symptoms. However, the majority of patient were diagnosed several years after the onset of neurological symptoms and hence therapy was delayed and commonly started after the age of four years. Though, intravenous and in some case intrathecal folinic acid therapy clearly improved clinical symptoms, all patients kept residual symptoms such as epilepsy and developmental delay. The fact that presymptomatic therapy prevents patients from developing any clinical symptoms and folinic acid can be provided at moderate costs, predestine FRα deficiency and other disorders of folate metabolism with CFD for genetic newborn screening.

Reference: Dreha-Kulaczewski et al., J Inherit Metab Dis. 2024, 47(2):387-403