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Characterizing Blood-Brain Sterol Pathways in Individuals with Deficient Sterol 27-Hydroxylase (CYP27A1) Enzyme Activity

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Abstract

Aberrant cholesterol metabolism is thought to play an important role in brain pathophysiology for many neurodegenerative disorders. How sterol metabolism impacts cerebral accumulation of toxic sterol species is not fully characterized. The brain houses 20-25% of total body cholesterol in a de novo synthesized pool unable to traverse the BBB. Formation of 7a-hydroxy-3-oxo-4-cholestenoic acid (7-HOCA) by the sterol 27-hydroxylase (CYP27A1) enzyme is one route of cerebral cholesterol removal, with flux of 7-HOCA demonstrated to occur across the BBB into the periphery. Deficient CYP27A1 activity is associated with cerebrotendinous xanthomatosis (CTX); a rare genetic disorder that can cause irreversible neurological decline associated with formation of cerebellar xanthomas, consisting mostly of cholesterol and a saturated analogue, cholestanol. Xanthomas can also form on tendons in CTX, including the Achilles tendon. In CTX a 7-HOCA precursor, 7α-hydroxy-4-cholesten-3-one (7αC4) is markedly elevated and can be converted to cholestanol, resulting in accumulation of this sterol. Peripheral 7αC4 readily crosses the BBB, and elevated cerebral 7αC4 is thought to contribute to cholestanol accumulation in the brain. In this study, sterols were measured in the blood and CSF of CTX patients and healthy controls. In addition, an atypical patient with putative CTX genotype and large tendon xanthomas, but with normal cholestanol and healthy brain function, was studied. 7αC4 was elevated in CTX compared to control plasma, with an intermediate 7αC4 level found in the atypical patient. 7-HOCA was <2mg/ml in CTX compared to 21-107ng/ml in control plasma, with 4ng/ml found in the atypical patient. 7-HOCA was not detectable in CTX CSF compared to 5652,920ng/ml in controls and 412ng/ml in the atypical patient. We hypothesize the atypical CTX case may be a result of residual CYP27A1 activity that allows adequate conversion of 7αC4 to 7-HOCA to prevent cholestanol accumulation in the brain and periphery as normally occurs in CTX.