Evaluation of the physiopathology of the allan-herndon-dudley syndrome. A characterization of double knock-out mice model of the disease.

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Keywords: Allan-Herndon-Dudley syndrome, hypothyroidism, synaptogenesis, microglia, astrocyte.

Thyroid Hormones (THs, T4 and T3) are essential in the development of the brain, regulating processes such as differentiation of neural cells and synaptogenesis. THs are secreted into the blood from the thyroid gland, mainly as T4, which is converted into T3, the nuclear active form, by the enzyme deiodinase 2 (DIO2), to exert genomic actions. Allan-Herndon-Dudley Syndrome (AHDS) is associated to a X-linked condition caused by mutations in monocarboxilate transporter 8 (MCT8), a transmembrane transporter highly specific for THs. AHDS is characterized by an endocrine and a neurological syndrome with congenital hypotonia that progresses to spasticity with severe psychomotor impairment. Evidences strongly suggest that the neurological syndrome in MCT8 deficiency is mainly due to a brain hypothyroidism, since the access of THs across brain barriers is impaired.

We analyzed the expression of synaptic scaffold proteins and the expression of different proteins in different populations of nerve cells in MCT8-deficient brain samples from an 11-year-old subject, in comparison to a control subject of the same age. In parallel, we studied the synaptogenesis markers distribution in neurons and the expression of different proteins in nerve cells in double knock-out mice for Mct8 and Dio2 brains, as a model for the disease. Protein expression was analyzed by immunohistochemistry. Our results showed a decreased expression of most of the synaptic proteins in the MCT8-deficient human brain in comparison to the control brain. To characterize glial cells, we evaluated the expression of GFAP, and we observed an increase in the number of astrocytes. Additionally, to evaluate microglial cells, we analyzed the expression of Iba-1. Our results revealed an increase in the number of Iba-1 immunopositive cells in the MCT8-deficient human brain. We also observed an increase in the number of GFAP immunopositive astrocytes in the cerebral cortex of Mct8/Dio2 knock-out mice. Regarding microglial cells, our results revealed an increase in the number of Iba-1 positive cells, in the cerebral cortex and hippocampus of Mct8/Dio2 knock-out mice. To differentiate resting and reactive microglial cells, we studied CD68 expression, a membrane protein much more abundant in reactive microglia cells. Our results showed a significant increase in the expression of this protein in the brain of the double knock-out in comparison to the wild-type mice. Our results suggest that synaptic transmission could be altered in patients with MCT8 deficiency, and the characterization of nerve cells suggests an inflammatory response due to MCT8 deficiency, what could be related to the psychomotor delay.

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Published May 18, 2018.
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Editor: Name of the editor here.
Funding: Funding explanation.
Competing Interests: Competing interest explanation.