The basal ganglia: a new possible therapeutic target in MCT8 deficiency

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The Allan-Herndon-Dudley syndrome is a rare disease caused by mutations in the gene *SLC16A2*, which codifies for the specific thyroid hormone cell-membrane transporter monocarboxylate transporter 8 (MCT8).

The altered expression of MCT8 leads to a singular scenario of prenatal brain hypothyroidism that is thought to underlie a dramatic neurological postnatal phenotype of developmental retardation, hypotonia and epilepsy. These clinical features start in the early infancy. Spastic tetraplegia, intellectual disability and paroxysmal dyskinesias appear posteriorly. The mechanisms underlying these clinical manifestations are poorly understood and, subsequently, a rational basis for a targeted, symptomatic therapy is still lacking.

The severe impairment in motor control of these patients, as well as the learning problems, points to basal ganglia dysfunction. Thus, we have analyzed human paraffin-embedded brain sections taken from necropsies of MCT8-deficient and control patients and we have immunohistochemically stained them to detect the MCT8 transporter, structural cell and synaptic proteins and a series of striatal markers.

Our results provide neuroanatomical evidence for severe structural and neurochemical deficiencies that might well explain the poor regulatory control of excitatory-inhibitory balance in basal ganglia microcircuitry and the extrapyramidal signs in patients affected by MCT8 mutations. This study, and others with more cases, could be the conceptual basis for further studies with '*in vivo*' non-invasive neuroimaging techniques to facilitate a rational improvement of the current symptomatic drug therapies for this disease.