Movement Disorders
CLINICAL PRACTICE
EDITORIAL COMMENTARY

Commentary: GM1-Gangliosidosis Type III Associated Parkinsonism

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This case displays a complex early-onset neurological phenotype with cognitive decline, supranuclear ophthalmoplegia, anarthria associated with risus sardonicus, progressive parkinsonism-dystonia, and spasticity.[1] Whilst acquired (hypoxic, infectious, toxic, neoplastic) causes should be considered, the positive family history of a similarly (but more mildly) affected sibling and relatives with parkinsonism strongly suggests a genetic etiology with possible autosomal recessive or mitochondrial inheritance. Although the phenomenology is suggestive of Wilson's disease, there is no corroborative evidence of copper accumulation in serum, urine, or neuroimaging studies. Juvenile Huntington's and *GCH1*-related disease should also be considered, as well as other rare genetic causes of juvenile parkinsonism-dystonia such as *PRKN*, *DNAJC6*, *ATP1A3*, *ATP13A2*, and *FBXO7*. Disorders of Neurodegeneration with Brain Iron Accumulation (NBIA), manganese transportopathies, and mitochondrial disorders are also potential differential diagnoses here.

For this case, a major diagnostic clue is provided by neuroimaging studies; bilateral posterior putaminal hyperintensities on T2-weighted MRI images are highly suggestive of a metabolic etiology such as GM1 gangliosidosis type III or glutaric aciduria type 1.[2] Although not undertaken for this patient, iron-sensitive neuroradiological sequences would also be of interest, to look for a "wish bone sign".[3]

Exome sequencing confirmed GM1 gangliosidosis type III; whilst the proband has many classical disease features (typical age of onset, progressive movement disorder, cognitive decline, T2-weighted neuroradiology findings), the presence of prominent parkinsonism and supranuclear ophthalmoplegia, and lack of skeletal abnormalities and generalized dystonia are somewhat atypical.

In conclusion, this informative case demonstrates (1) the phenotypic variability of GM1 gangliosidosis type III; (2) that this condition should be considered in the differential diagnosis of juvenile-onset parkinsonism-dystonia, even without a skeletal phenotype; and (3) how awareness of the distinct MRI signs associated with a condition can accelerate clinical diagnosis.

Video 1. Full video from the 2020 Video Challenge discussion of this case.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13301

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