

HOPS-Associated Neurological Disorders: Lysosomal Dysfunction as an Emerging Concept Underlying Dystonia

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Dystonia is a clinical symptom thought to emerge from brain network dysfunction involving abnormal cortical excitability, plasticity, and sensory dysfunction within the somatosensory cortex, basal ganglia, and cerebellum. Although these abnormalities have repeatedly been identified in different entities, presenting with isolated and combined dystonia, common pathophysiological concepts underlying dystonia, such as endoplasmic reticulum function, gene transcript modulation during neurodevelopment and nigrostriatal dopaminergic signaling are only beginning to emerge.¹ As in other fields of neurology, the identification of causative genetic mutations has tremendously contributed to elucidating the underlying pathophysiology.

Recent publications reported mutations in genes encoding central parts of the homotypic fusion and protein sorting (HOPS) complex to cause dystonia of various degrees,^{2–5} which has led Monfrini and colleagues⁶ to group these disorders under the term HOPS-associated neurological disorders. Cellular protein homeostasis is critically dependent on adequate cell clearing mechanisms, relying on the fusion of endosomes and autophagosomes with lysosomes for protein degradation. The HOPS complex physiologically facilitates the fusion of lysosomes with autophagosomes and, therefore, is critically involved in this process.⁶ Thus far, three of the six vacuolar protein sorting-C proteins, forming the HOPS complex, have been identified to cause autosomal-dominant (VPS16)² or autosomal-recessive (VPS11, VPS16, and VPS41)^{3–5} dystonia. In the majority of cases, dystonic features first presented in infancy (VPS41)² or adolescence (VPS11)^{2,4} with predominant craniocervical and bulbar involvement, generalizing in most cases, whereas onset in VPS11 was in adulthood with early generalization.⁴ Additional symptoms have been described for manifestations in infancy, ranging from epilepsy, spasticity and polyneuropathy to optic neuropathy (VPS11 and VPS41). Cell-culture experiments and electro-microscopy studies from patient-derived fibroblasts document impairment of the autophagolysosome for all three gene mutations.^{2,4} Together with the generation of a homozygous mutant mouse line with

impaired motor function,³ this establishes a loss-of-function mechanism behind these mutations.⁶

Thus far, lysosomal storage disorders have been reported to cause combined dystonia, which has been particularly recognized in cases of Niemann-Pick type C, GM1, and GM2 gangliosidosis, fucosidosis and adult non-neuropathic Gaucher's disease.⁷ The identification of mutations in HOPS-associated genes as well as in WDR45, ATP13A2, VAC14, IRF2PBL, and SQSTM1—all of which encode proteins of the endolysosomal and autophagy pathway, causing a predominant dystonic phenotype—further establishes the growing link between lysosomal dysfunction and dystonia.⁶

It remains to be seen in how far lysosomal dysfunction can be identified as a contributing or even causative factor, not only in selected hereditary and combined, but also in sporadic and isolated dystonia in the future. Similarly, the mechanism by which lysosomal dysfunction causes dystonia on a network-basis, and whether there is a common endophenotype for this entity, which would lend itself for screening, is currently unknown. Nevertheless, this could potentially open novel, causative treatment avenues targeting lysosomes⁸ for a syndrome so far depending on symptomatic treatment only.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Relevant disclosures and conflict of interest are listed at the end of this article.

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