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Parkinsonism in individuals with genetic neurodevelopmental disorders: A systematic review

Background: While genetic brain disorders are traditionally dichotomized into neurodevelopmental and neurodegenerative disorders, there is increasing evidence of an overlap in its clinical and genetic determinants. Indeed, with advances in clinical genetic testing for neurologic disease, the number of genetic neurodevelopmental disorders (GNDs) associated with parkinsonism is growing fast. We aim to provide a comprehensive overview of reports on parkinsonism in GNDs and summarize findings related to genetic diagnosis, clinical features and proposed disease mechanisms in addition to implications for clinical practice and future research.

Methods: We conducted a systematic literature review, and searched PubMed and Embase on June 15, 2021. General search terms for GNDs, and a list of neurodevelopmental disorders as per the Human Phenotype Ontology, were combined with terms for parkinsonism. Study characteristics and descriptive data on GNDs and parkinsonism were extracted from the included articles. The protocol was registered in PROSPERO (CRD42020191035).

Results: Our search yielded 208 reports, describing 69 different GNDs in 422 patients with parkinsonism. The five most reported GNDs from most to least frequent were: 22q11.2 deletion syndrome, beta-propeller protein-associated neurodegeneration, Down syndrome, cerebrotendinous xanthomatosis and Rett syndrome. Median age of motor onset was only 26 years. Response to antiparkinsonian medication, and results of dopaminergic imaging were often supportive of Parkinson's disease. Interestingly, neuropathology results showed neuronal loss in the majority of cases reported, indicative of an overlap in neurodevelopmental and neurodegenerative processes. Proposed disease mechanisms included aberrant mitochondrial function, autophagic-lysosomal system, neurotransmitter metabolism, endosomal trafficking and the ubiquitin-proteasome system.

Conclusion: Parkinsonism has been reported in many genetic neurodevelopmental disorders. The combination of parkinsonism and a neurodevelopmental disorder may prompt physicians to consider genetic testing, facilitating precision medicine. Further study of parkinsonism in genetic neurodevelopmental disorders may provide new insights into the mechanisms causing parkinsonism, crucial for the development of novel treatments.