Mitochondrial dysfunction and pathophysiology of Charcot-Marie-Tooth disease involving GDAP1 mutations

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Résumé en anglais	Charcot-Marie-Tooth (CMT) disease represents a large group of clinically and genetically heterogeneous disorders leading to inherited peripheral neuropathies affecting motor and sensory neurons. Mutations in the ganglioside-induced differentiation-associated-protein 1 gene (GDAP1), which encodes a protein anchored to the mitochondrial outer membrane, are usually associated with the recessive forms of CMT disease and only rarely with the autosomal dominant forms. The function of GDAP1 is not fully understood but it plays a role in mitochondrial dynamics by promoting fission events. We present an overview of GDAP1 and the corresponding protein together with the complete spectrum of the 41 gene mutations described so far. We examine the relationship between the genotype and the phenotype in the various forms of CMT disease related to GDAP1 mutations, and discuss the pathophysiological hypotheses that link peripheral neuropathies to mitochondrial dysfunction and GDAP1 mutations. The meta-analysis of the literature reveals the great heterogeneity of phenotypic presentations and shows that the recessive forms of CMT disease, i.e. CMT4A and AR-CMT2, are far more severe than the dominant form, i.e. CMT2K. Among patients with recessive forms of the disease, those carrying truncating mutations are more seriously affected, often becoming wheelchair-bound before the end of the third decade. At the neuronal level, GDAP1 mutations may lead to perturbed axonal transport and impaired energy production as in other neurodegenerative diseases due to mutations in genes involved in mitochondrial dynamics.
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