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Survey of tauopathy in mitochondrial protein associated neurodegeneration

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Abstract

Tauopathy and a-synucleinopathy often occur together in human brain diseases but most commonly in the context of β-amyloidosis. Tauopathy induced by a-synucleinopathy in the absence of β-amyloid has been demonstrated in vitro and in cultured cells but compelling examples of this in human disease are rare and limited largely to instances of familial Parkinson's disease due to mutations in the a-synuclein gene. Mitochondrial protein-associated neurodegeneration (MPAN) due to mutations in C19orf12 produces neurodegeneration with brain iron accumulation as well as widespread a-synucleinopathy. Four patients with genetically confirmed MPAN were referred for brain autopsy and a complete histologic and immunohistochemical evaluation was undertaken for lesions and proteinopathies of common neurodegenerative diseases as well as the specific reported lesions of MPAN.All patients had hallmark pathologic features of MPAN including atrophy, gliosis, and iron accumulation involving the globus pallidus as well as abundant a-synucleinopathy manifest as Lewy bodies and neurites thoughout the brain. Tauopathy was present in each case with neurofibrillary tangles distributed in Braak stages I to V with pretangles and more widely distributed tau-positive dystrophic neurites. The distribution and regional burden of tauopathy was less than that of a-synucleinopathy in each case. β-amyloid or TDP-43 abnormalities were not identified in any case. The lesional burden and distribution in MPAN are consistent with a pathogenetic model in which dysmetabolism of a-synuclein is sufficient, in the absence of other common neurodegenerative pathologies, to induce tauopathy. Study of rare familial diseases such as MPAN may enhance our understanding of the pathogenesis of common idiopathic neurodegenerative diseases.