INTENSIFIED AND COMBINED NEURODEGENERATION IN E200K GENETIC CREUTZFELDT-JAKOB DISEASE

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Introduction: The E200K mutation is the most frequent prion protein gene (PRNP) mutation associated with genetic Creutzfeldt-Jakob disease (CJD). It is thought to have overlapping features with sporadic CJD, yet comparative neuropathological studies have not been reported.

Aims: To describe salient and concomitant neuropathological alterations in E200K genetic CJD.

Methods: We performed a comprehensive neuropathological and biochemical study of brains from 39 individuals carrying the E200K PRNP mutation.

Results: Although there was a relatively uniform anatomical pattern of tissue lesioning, the deposition of disease-associated PrP was influenced by the codon 129 constellation, including different or mixed types of PrP\textsuperscript{res} detected by immunoblotting. We detected unique intraneuronal PrP deposition involving also brainstem nuclei. In addition, parenchymal amyloid-β was observed in 53.8% of cases, amyloid angiopathy (Aβ) in 23.07%, phospho-tau immunoreactive neuritic profiles in 92.3%, neurofibrillary degeneration in 38.4%, new types of tau pathology in 33.3%, and Lewy-type α-synuclein pathology in 15.4%.

Conclusions: Although age-associated and additional neurodegeneration has been described in prion diseases, we demonstrate intensified and combined neurodegeneration in a genetic prion disease due to a single point mutation. The E200K mutation may be an important model to evaluate the molecular interplay between neurodegeneration-associated proteins.