NEUROPATHOLOGICAL ANALYSIS OF GENETIC PRION DISEASE ASSOCIATED WITH THE RARE E196K MUTATION

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Introduction: Genetic forms of human transmissible spongiform encephalopathies are linked to mutations in the prion protein gene (PRNP). Some forms closely resemble sporadic Creutzfeldt-Jakob disease (sCJD) while others are distinct regarding disease onset/duration, clinical signs and neuropathological findings. Information on the rare E196K PRNP mutation so far was limited to clinical and genetic data.

Aims: To provide a comprehensive account of the neuropathological and molecular phenotype related to the rare E196K mutation.

Methods: Four patients carrying the rare E196K mutation identified in the German CJD surveillance study were analyzed neuropathologically and by biochemical PrPSc typing.

Results: Two patients (codon 129 MM and MV, respectively) resembled the MM/MV-1 subtype of sCJD, one patient (codon 129 VV) resembled the sCJD VV-2 subtype, whereas patient 4 presented with an atypical neuropathological phenotype. Notably, densitometric analysis of the PK-resistant bands revealed a significant underrepresentation of the non-glycosylated form in all brain regions in all four patients carrying the E196K mutation, irrespective of the PrPSc type and neuropathological phenotype.

Conclusions: Our data indicate that

(i) the E196K mutation is causally linked to human prion disease,

(ii) a complex phenotypical spectrum related to this mutation exists which includes cases with atypical neuropathology and cases presenting with features resembling various subtypes of sCJD corresponding to the codon 129 polymorphism of the prion protein gene.