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Poster Session PPo5: Basic Mechanisms of Neurodegeneration and Pathology

PPo5-1: Deposition of Multiple Proteins in E200K Genetic Creutzfeldt-Jakob Disease

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Key words: E200K mutation, prion protein gene, tau, amyloid-beta, a-synuclein

The E200K mutation is the most frequent prion protein gene (PRNP) mutation detected worldwide that associates with genetic Creutzfeldt-Jakob disease (CJD). We performed a comprehensive neuropathological and biochemical study of brains from 39 individuals carrying the E200K PRNP mutation. 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 PrPres detected by immunoblotting. Some PrP deposition features have not been described in sporadic CJD, like prominent intraneuronal PrP deposition involving also brainstem nuclei. In addition, parenchymal amyloid-β was observed in 53.8% of cases, amyloid angiopathy (A) 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%. TDP-43 and FUS immunoreactive protein deposits were not observed. Although age-associated and additional neurodegeneration has been described in prion diseases, here we demonstrate intensified and combined neurodegeneration in a genetic prion disease due to a single point mutation, which might become an important model to decipher the molecular interplay between neurodegeneration-associated proteins.

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PPo5-2: Temporal Kinetics of Prion Protein Accumulation and Its Effect on Neurotransmitters in the Cerebellum of Guinea Pigs Infected with BSE Prion

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Key words: BSE, guinea pig, cerebellum, GABAergic synapse, glutamatergic synapse

Cerebellar lesions in guinea pigs (GPs) inoculated intracerebrally with BSE prion are characterized by severe atrophy of the cerebellar cortex associated with PrPBSE accumulation. In this study, we examined the temporal kinetics of PrPBSE accumulation in the cerebellum of GPs infected with BSE prion and an immunohistochemical fluctuation of GABAergic and glutamatergic synapses using antibody for the vesicular transporter. The GPs inoculated intracerebrally with PrPBSE were sacrificed under anesthesia at 172, 203, 230, 263, 305, 312 and 323 dpi. Immunohistochemical analysis was carried out with anti-prion protein(mAb12F10), GFAP, Calbindin and MAP2 antibodies. For analysis of synapse expression, anti-synaptophysin, GABAergic synapse's marker (VGAT), glutamatergic synapse's marker (VGLUT1, VGLUT2) antibodies were used. In the GP control, VGLUT1 positive synapses were seen in the pontine nucleus and cerebellar cortex, while VGLUT2 positive synapses were seen in the pontine, olivary and cerebellar nucleuses and cerebellar cortex. VGAT positive synapses showed similar distribution as VGLUT2 positive synapses except in the pontine nucleus. PrPBSE accumulation was observed in the pontine and olivary nucleuses, and cortex of vestibulocerebellum at on early stage, and then seemed to extend throughout the whole brainstem and cortex of the cerebrocerebellum with time. In PrPBSE accumulated regions, VGLUT1 positive synapses apparently decreased, however, VLUT2 and VGAT positive synapses preserved a normal appearance. In the GPs experimentally infected with BSE, accumulation of PrPBSE were similar to the distribution of VGLUT1 positive glutamatergic synapses, and synapses diminution associated with PrPBSE seemed to reflect a decrease in VGLUT1 positive glutamatergic synapses.