Article: EPA-1718
Topic: E05 - e-Poster Oral Session 05: Childhood and Geriatry, Depression

NEUROPATHOLOGICAL ALTERATIONS IN FTD CASES WITH C9ORF72 MUTATION – NEW INSIGHTS

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A G4C2 repeat extension in the first intron of *C9ORF72* is the most common cause of familial frontotemporal dementia with and without motoneuron disease or atypical Parkinsonism. We recently found that the characteristic p62 positive/TDP43 negative neuronal cytoplasmic inclusions (NCIs) mainly seen in cerebellum und hippocampus consist of different dipeptide repeat proteins (DPRs) generated by an ATG independent translation of stable sense and antisense transcripts of the extended intron.

After creating specific antibodies against all potential DPRs resulting from different reading frames, we investigated their regional and cellular distribution pattern in the central nervous system of autopsy cases with *C9ORF72* mutation by immunohistochemistry.

Aggregates of all DPRs were seen in neuronal cell bodies and processes. Glycine-alanine and glycine-prolin DPRs dominated. NCIs were abundant in all neocortical areas, in the hippocampal formation and in cerebellum, less frequent in subcortical nuclei, and rare in brain stem and spinal cord following a rostro-caudal gradient. Different DPRs were found in the same NCI. The regional distribution pattern of NCIs was similar in all clinical subtypes, and did not directly correlate with neurodegeneration. DPRs and TDP43 that usually also aggregates in *C9ORF72* mutation cases were rarely co-localized in the same NCI. In case of co-localization DPR proteins formed a central core surrounded by TDP43.

The detection of DPR inclusions directly connects the mutation with specific neuropathological alterations. The formation of DPR inclusions seems to precede the formation of TDP43 inclusions. If there is a neurotoxic effect of DPRs, DPR inclusions might be neuroprotective.

https://doi.org/10.1016/S0924-9338(14)78857-1 Published online by Cambridge University Press