

<シンポジウム 07—4> Atypical types of dementia 非典型認知症

Dementia with motor neuron disease

Michael J. Strong¹⁾, Wencheng Yang¹⁾, May Gohar²⁾ and Wendy L. Strong²⁾

(臨床神経 2011;51:935)

Background

The neurodegenerative process of amyotrophic lateral sclerosis (ALS) includes both selective degeneration of motor neurons and one or more syndromes of frontotemporal dysfunction (e.g., behavioural (ALSbi) or cognitive (ALSci) syndromes, a frontotemporal dementia (ALS-FTD)). There is widespread degeneration of the frontal, temporal and to a lesser extent parietal lobes in association with TDP-43 immunoreactive pathology. We have shown that tau protein metabolism is also altered in ALSci and now describe the topographic distribution of tau pathology in ALS.

Methods & Results

Tau is hyperphosphorylated (pThr175-tau) in ALSci and is associated with an upregulated of GSK-3b activity. We generated novel rabbit polyclonal antibodies to three tau phospho-epitopes (pSer208, 210, pThr217 and pThr175) and

demonstrated pathological tau aggregates in both ALSci and ALS. The pattern of deposition suggests that phylogenetically more primitive regions (amygdala, entorhinal cortex, hippocampus) are involved prior to more anteriorly placed regions (i.e., anterior cingulate gyrus). Tau pathology was prominent in astrocytes. Neuronal pThr175-tau immunoreactive aggregates were associated with an up-regulation of TDP-43 expression but not with TDP-43 aggregates. Transient transfections with pseudo-phosphorylated tau (Asp-Thr 175-tau) induces tau fibrils and an enhanced rate of cell death that could be inhibited the inhibition of GSK-3b activation.

Conclusions

While ALSci shows pathological processing of both TDP-43 and in tau protein, our observations suggest that ALSci is primarily a disorder of tau protein metabolism. This provides a basis on which to develop novel ALS therapies directed towards cognitive impairment.

¹⁾Department of Clinical Neurological Sciences, The Schulich School of Medicine & Dentistry, The University of Western Ontario [Canada]

²⁾The Robarts Research Institute, Schulich School of Medicine & Dentistry, The University of Western Ontario
(Received: 19 May 2011)