Distinct developmental expression of phosphorylated Tau in Down syndrome brains

Jasna Jarc BA, Ivan Milenkovic MD PhD
Institute of Neurology, Medical University of Vienna, Vienna, Austria

Introduction
The concept of our research is based on the link between disorders of neural development and age-related neurodegenerative diseases. The hallmark of AD is deposition of misfolded tau and Aβ proteins. Interestingly, pathologic phosphorylation of tau protein is reported to be transiently present in the normal developing brain. Thus, the aim of this research was to compare the phosphorylation of tau proteins during normal development and developing brains of individuals with DS.

Results
We distinguished different immunostaining patterns & changes in the spatiotemporal distribution of tau immunoreactivities (IR) in DS individuals and controls.

Fig. 4. Different tau markers in human MCP during P2 of normal development compared to DS brains: Critical reduction in AT6 and AT180-IR in DS brains in P2 in the MCP area.

Fig. 5. Two different tau markers in human Hippocampal structures during P2 of normal development compared to DS brains: No phosphorylation observed with AT8.

Fig. 6. Graph supporting the idea of possible sequential tau phosphorylation in the developing human brains: regional differences in tau phosphorylation the earliest IR observed in rhombencephalon (MCP), followed by rostrally located brain structures (IC, SUB and CA1).

Conclusions and further directions
Our data strongly suggests:
1. Selective loss of tau phosphorylation at Ser-202 (AT8) and Thr-231 (AT180) are critically disturbed in individuals with DS. This effect was noted in the rhomboencephalic structures (Fig. 4), whereas in rostral brain areas (Fig. 5) no phosphorylation was observed. With exception of the subiculum, total amount of tau seemed not to significantly differ between groups.

Phosphorylation of tau is developmentally regulated and has an important role for brain physiology and brain development. It’s effect depends on the location of the site modified. Hyperphosphorylation disrupts tau’s normal function in regulating axonal transport and leads to the accumulation of neurofibrillary tangles (NFTs) and toxic species of soluble tau. It is one of the post-translational modifications of tau protein and induces cognitive impairment seen in AD patients.

AD is a neurological disorder that causes memory (working, spatial, recognition) and associative learning deficits, emotional problems and impaired reasoning. In AD, tau is hyperphosphorylated and cannot stop irrelevant information flowing to the brain causing overloading that leads to inflammation, NFTs and death of neurons.

Methodology
We compared the patterns of tau phosphorylation of 26 fetal cases diagnosed with DS and 29 age-matched cases of normal brain development. After immunohistochemistry, we precisely inspected the scans of glass slides for the density of 6 antibodies, either phosphorylation dependent (AT100, AT270, AT180 and AT8) or independent (HT7 and polyclonal anti-human tau antibody (TT2)). We distinguished between 3 developmental periods – period 1 (P1: 14-16 gestational week (GW)), period 2 (P2: 17-28 GW) and period 3 (P3: 29 GW onwards).

Areas inspected:
- Hippocampus (CA1 and Subiculum) ➔ navigation and memory functions (spatial and declarative memory)
- Cerebellum (Medial Cerebellar Peduncle (MCP)) ➔ motor learning
- Internal Capsule ➔ an important cross-path in human brain

Phosphorylation of tau protein associated as a protective mechanism in the presence of toxic, C-terminally truncated tau in Alzheimer’s disease. INTECH Open Access Publisher.

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References