

ARE THE TAUOPATHIES A SPECTRUM OR DISTINCT DISEASES: DISTINCT DISEASES

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Tauopathies are clinically, morphologically, and biochemically heterogeneous neurodegenerative diseases characterised by the deposition of abnormal tau protein in the brain. The neuropathological phenotypes are distinguished based on the involvement of different anatomical areas, cell types and presence of distinct isoforms of tau in the pathological deposits. Neuropathological phenotypes comprise Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), primary age-related tauopathy (PART), formerly called also as neurofibrillary tangle-only dementia, and globular glial tauopathy (GGT) (1). Mutations in the encoding gene of the microtubule associated protein tau (*MAPT*) are associated with frontotemporal dementia and parkinsonism linked to chromosome 17. In addition, further neurodegenerative conditions with diverse aetiologies may be associated with tau pathologies. These include Alzheimer's disease (AD), Down syndrome, Lewy body disorders, familial british and danish dementia, prion diseases, neurodegeneration with brain iron accumulation associated with certain gene mutations, Niemann-Pick disease, postencephalitic parkinsonism, Parkinsonism-dementia complex of Guam, cerebrotendinous xanthomatosis, chronic traumatic encephalopathy, tauopathies associated with *TARDBP*, *LRRK2*, *alpha-Synuclein*, *GRN*, or *C9orf72* gene mutations, or with certain forms of mental retardation (eg. *SLC9A6* gene mutation), myotonic dystrophy, or subacute sclerosing panencephalitis (1).

Tau is a microtubule-associated protein (MAP). In the adult human brain six isoforms of tau are expressed by alternative splicing from the *MAPT* gene located on chromosome 17q21. The six isoforms differ from each other by the presence or absence of 29- or 58-amino acid inserts in the N-terminal part and by the presence of either three (3R) or four (4R) tandem repeat sequences of 31 or 32 amino acids. In the normal human brain similar levels of 3R and 4R isoforms are expressed. Tau filaments in patients affected by tauopathies are composed of either 3R- or 4R-tau or both, reflecting the biochemical heterogeneity of tauopathies; furthermore it is the basis of current molecular classification of tauopathies (1). Patterns of insoluble tau observed in Western blots are I) major bands at 60, 64, and 68 kDa (e.g. in AD, PART); II) bands at 64 and 68 kDa (e.g. in 4R predominant tauopathies, AGD, PSP, CBD, GGT); and III) bands at 60 and 64 kDa (e.g. in 3R predominant tauopathies, PiD). The most important posttranslational modification of tau in disease is hyperphosphorylation. Further modifications like acetylation of tau may also prove to be important for the neuropathological and *in vivo* biomarker diagnostic practice.

The cellular distribution of immunoreactive structures visible using immunohistochemistry for phospho-tau or isoform specific antibodies also distinguish tauopathies even if there are overlapping features (1). Tau immunoreactivity related to neurons include the 1) pretangles, 2) neurofibrillary tangles, 3) Pick bodies, 4) spherical cytoplasmic inclusions, 5) dystrophic neurites, 6) threads, and 7) grains. Astrocytes show a variety of tau immunoreactivities, often labelled with different terminologies. For the diagnostic practice differentiation of tufted astrocyte (PSP) from astrocytic plaque (CBD) is the most relevant. Further tau immunoreactivities (AT8) comprise thorn-shaped and the recently characterised globular astroglial inclusions (GAI). In addition, diffuse fine granular tau immunopositivity along astrocytic processes are observed in elderly individuals in the temporal cortex. Importantly, tau phosphorylation sites, conformational modifications, tau truncation, and ubiquitination in astrocytes differed between various types of tauopathies. Phospho-Tau immunoreactivity in oligodendrocytes comprises coiled bodies and globular oligodendroglial inclusions (GOIs). While coiled bodies can be seen in some tauopathies, GOIs are characteristic for GGTS. Microscopic evaluation of phospho-tau immunostained sections reveals that tau pathologies are either neuronal, mixed neuronal/ glial or glial predominant. The anatomical distribution of the tau pathology and involvement of the white matter also helps to distinguish tauopathy forms. Furthermore, tau inclusions are different in their state of fibrillization, thus they are distinctly stained using Gallyas or Bielschowsky silver stainings or using antibodies detecting only the fibrillar form of tau protein.

There are further observations, which support the concept that tauopathy entities, defined currently on a morphological/biochemical level, are distinct:

1) Biochemical comparison of PSP and CBD (both 4R tauopathies but showing distinct cytopathologies) shows that on immunoblots of sarkosyl-insoluble brain extracts, a 33kDa band predominated in the low molecular weight tau fragments in PSP, whereas two closely related bands of approximately 37kDa predominated in CBD (2).

2) Experimental injection of brain extracts from humans who had died with various tauopathies into the hippocampus and cerebral cortex of ALZ17 mice recapitulated the hallmark lesions of AGD, PSP and

CBD. This supports the concept that tauopathy entities may represent different strains of disease (3). A further study showed differential induction and spread of tau pathology in young PS19 tau transgenic mice following intracerebral injections of pathological tau from AD or CBD brains (4). 3) Ultrastructural examinations show that even seemingly similar cytopathologies are distinct as exemplified by the difference of pretangles in AD and CBD (5).

Regarding the clinical symptoms; in this aspect the neuropathologically defined tauopathy groups are indeed difficult to diagnose. But this is generally true for neurodegenerative diseases, that different disorders can affect the same anatomical regions. The clinical symptoms are determined by the system affected and do not unequivocally reflect the molecular pathologic background. Thus not only tauopathies, but also other forms of neurodegenerative disorders associated with other conformationally altered proteins may show similar clinical symptoms (1).

In summary, although tauopathies show overlapping clinical symptoms, they show distinct biochemical and morphological (ultrastructural) features, supported by experimental observations on spreading of disease suggesting distinct strains of disease.

References

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