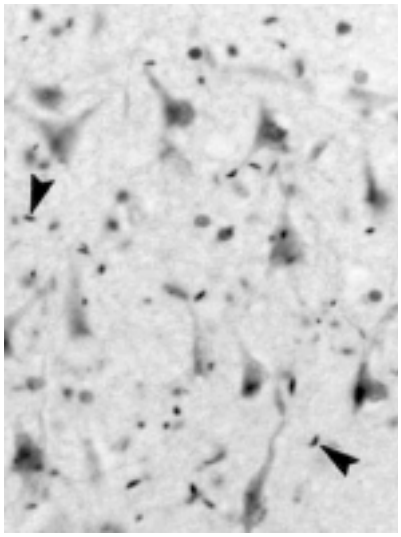
Pathological tau proteins in argyrophilic grain disease

Argyrophilic grain disease (AGD) is an adult-onset progressive dementia (also called Braak's dementia) that is characterised by spindle-shaped argyrophilic grains found within neuronal processes.[1] Argyrophilic grains are mainly found in the CA1 subfield of the cornu ammonis, entorhinal and transentorhinal cortices, the amygdala, and the hypothalamic lateral tuberal nuclei (figure). In addition, tau-positive oligodendrocytes ("coiled bodies") are seen in the white matter and deep cortical layers.

In a study of 2661 non-selected brains at autopsy, Braak and Braak[2] found AGD in 5% of individuals aged between 51 and 96 years. The finding that 6% of individuals from the same population had fully-developed Alzheimer's disease supports the view that AGD is an underestimated cause of dementia in old patients. Besides its frequent occurrence, AGD merits attention due to its potential to cause marked cognitive decline. The clinical features of AGD depend on the quantity and anatomical distribution of argyrophilic grains. Recent studies have highlighted memory disturbance and personality change characterised by emotional imbalance with aggression or ill temper as symptoms of the disease.[3]

Argyrophilic neurofibrillary lesions are not only found in AGD but also in a number of other neurodegenerative disorders, including Alzheimer's disease, Pick's disease, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Ultrastructurally these lesions contain straight and paired helical filaments composed of the microtubule-associated protein tau in a hyperphosphorylated state. The human tau primary transcript contains 13 exons of which exons -1 and 14 are not translated. Exons 1, 4, 5, 7, 9, 11, 12, and 13 are constitutive, whereas exons 2, 3, and 10 alternatively splice to produce a family of six isoforms, which range from 352 to 441 amino acids.[4] Tau proteins bind microtubules via highly-conserved repetitive domains (R1–R4) that regulate the rate of microtubule polymerisation and are encoded by exons 9 to 12. Alternative splicing of exon 10 gives rise to tau isoforms with 3 (with exon 10) or 4 (without exon 10) repeats in the microtubule-binding domain—so-called three-repeat (3R) tau and four-repeat (4R) tau.[4] Tau protein accumulates within neurons and glia in neurodegenerative diseases in a disease-specific manner. Both 3R and 4R tau isoforms are present in various proportions in Alzheimer's disease, Down's syndrome, and some families with frontotemporal dementia with parkinsonism due to mutations in the tau gene on the chromosome 17 (FTDP-17). 3R tau predominates in Pick's disease whereas 4R tau predominates in PSP, CBD, and some forms of FTDP-17.



Courtesy of Goran Simic

Argyrophilic grains in the entorhinal cortex

Although it is known that argyrophilic grains contain hyper-phosphorylated tau, the isoform composition of the grains has not been clarified. This is presumably because the grains have not been isolated to homogeneity and biochemical analysis is confounded by concomitant neurofibrillary pathology. In a recent study, Togo and colleagues[5] deciphered the nature of pathological tau proteins in a series of seven individuals with AGD who had a range of neurofibrillary pathology. To determine the isoform composition of argyrophilic grains the investigators did western blot analysis of sarkosyl-insoluble tau together with immunocytochemistry with newly developed monoclonal antibodies specific to 3R and 4R tau. The researchers have shown, both biochemically and immunocyto-chemically, that argyrophilic grains are composed of hyperphosphorylated tau enriched in 4R tau. AGD can be therefore considered a sporadic 4R tauopathy, sharing a common genetic risk factor with PSP and CBD.

Over-representation of an extended tau H1 haplotype and H1/H1 genotype has been recognised in both PSP and CBD. Although the study by Togo and colleagues showed a trend for increased H1 haplotype, the small sample size and relatively high frequency of H1 in the control population limited the conclusions. However, the data obtained, together with the high frequency of AGD in PSP and CBD (about 20% of patients with PSP, and 40% of patients with CBD, have AGD) and the fact that "grain-like" lesions in PSP and CBD are not restricted to the limbic lobe and hypothalamus, suggest that 4R tauopathies may represent a disease spectrum. The medial temporal lobe tauopathy seen in AGD is intermediate between the diffuse cortical and subcortical tauopathy of CBD and the more restricted basal ganglia and brainstem tauopathy of PSP.

It is hoped that more accurate biological analysis of CSF in the future will help to discriminate between tau protein types present in physiological conditions and tau released during the progression of a particular neurodegenerative disease.

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