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Neuropathology of Frontotemporal Lobar Degeneration–Tau (FTLD-Tau)

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Abstract

A clinically and pathologically heterogeneous type of frontotemporal lobar degeneration has abnormal tau pathology in neurons and glia (FTLD-tau). Familial FTLD-tau is usually due to mutations in the tau gene (*MAPT*). Even FTLD-tau determined by *MAPT* mutations has clinical and pathologic heterogeneity. Tauopathies are subclassified according to the predominant species of tau that accumulates, with respect to alternative splicing of *MAPT*, with tau proteins containing 3 (3R) or 4 repeats (4R) of ~ 32 amino acids in the microtubule binding domain. In Pick's disease (PiD), 3R tau predominates, whereas 4R tau is characteristic of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). Depending upon the specific mutation in *MAPT*, familial FTLD-tau can have 3R, 4R or a combination of 3R and 4R tau. PiD is the least common FTLD-tau characterized by neuronal Pick bodies in a stereotypic neuroanatomical distribution. PSP and CBD are more common than PiD and have extensive clinical and pathologic overlap, with no distinctive clinical syndrome or biomarker that permits their differentiation. Diagnosis rests upon postmortem examination of the brain and demonstration of globose tangles, oligodendroglial coiled bodies and tufted astrocytes in PSP or threads, pretangles and astrocytic plaques in CBD. The anatomical distribution of tau pathology determines the clinical presentation of PSP and CBD, as well as PiD. The basis for this selective cortical vulnerability in FTLD-tau is unknown.

Keywords

corticobasal degeneration; corticobasal syndrome; frontotemporal lobar degeneration – tau; Pick's disease; progressive supranuclear palsy; Richardson syndrome

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is a term for the group of non-Alzheimer degenerative dementias with focal cortical neuronal loss and gliosis (McKhann et al., 2001). It encompasses a range of different clinical syndromes [e.g., behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia (PNFA), semantic dementia (SD) and corticobasal syndrome (CBS)] and a range of different pathologies (Mackenzie et al., 2009). The most common is FTLD associated with TDP-43 pathology (FTLD-TDP), with tauopathies (FTLD-tau) considered slightly less common (Wider and Wszolek, 2008). This brief review summarizes the neuropathology of sporadic FTLD-tau.

Mutations in the gene for the microtubule associated protein tau (*MAPT*) account for most cases of familial FTLD-tau (Hutton et al., 1998). The reader is referred to recent reviews of this topic for more details (Forman et al., 2005, van Swieten and Spillantini, 2007).

Tau protein is the major structural protein of neurofibrillary tangles in Alzheimer disease (AD) (Grundke-Iqbal et al., 1986a). It is a heat-resistant phospho-protein that promotes microtubule polymerization and stabilization. Once considered to be relatively restricted to neurons (Binder et al., 1985), it is now known that tau accumulates not only in neurons in neurofibrillary tangles, but also in glia in a wide range of neurodegenerative disorders and in the aging brain. Disorders in which tau pathology is considered the major contributing factor to neurodegeneration are referred to as “primary tauopathies.” Tau protein in the brain is heterogeneous due to alternative splice forms, as well as post-translational modifications, including phosphorylation (Grundke-Iqbal et al., 1986b). Exon 10 of *MAPT* is alternatively spliced to generate tau species with either three or four conserved ~32 amino acid repeats in the microtubule binding domain of tau protein (Andreadis et al., 1992), referred to as 3R and 4R tau. There is preferential accumulation of 3R or 4R tau in various tauopathies, providing a biochemical subclassification of the tauopathies. In AD, neurofibrillary pathology is composed of an equimolar ratio of 3R and 4R tau (Goedert et al., 1989) (Table 1).

3R TAUOPATHIES

Pick’s disease (PiD)

PiD is a rare cause of frontal lobe dementia, accounting for less than 5% in autopsy series of dementia (Barker et al., 2002). It is classically associated with circumscribed “lobar” atrophy. The distribution of focal cortical degeneration determines the clinical presentation. Clinical presentation with bvFTD is seen in PiD with frontotemporal atrophy (Constantinidis et al., 1974), while frontoparietal atrophy presents with apraxia (Lang et al., 1994) and perisylvian atrophy with PNFA (Graff-Radford et al., 1990). When amnesic symptoms prevail, clinical diagnosis is often initially AD. It is a disorder that affects men and women equally and is usually associated with a “presenile dementia” with age of onset younger than 65 years. Mutations in the tau gene (*MAPT*) account for most pathologically confirmed cases of familial PiD (Murrell et al., 1999, Hogg et al., 2003, Bronner et al., 2005).

The cardinal neuropathologic features are circumscribed cortical atrophy associated with neuronal loss, gliosis and argyrophilic, round intraneuronal inclusions (Pick bodies). Pyramidal neurons in the hippocampus and granular neurons in the dentate fascia are particularly vulnerable (Fig. 1a). Pick bodies are composed of tau protein enriched in 3R tau, which can be shown with biochemical studies (Buee and Delacourte, 1999), or more recently with antibodies specific to tau isoforms (de Silva et al., 2006). They are argyrophilic on some silver stains (e.g., Bielschowsky (Fig. 1b)), but consistently negative with the Gallyas silver stain (Fig. 1c). A less specific feature of PiD is the ballooned neuron (also known as Pick cell (Fig. 1d)). Tau-immunoreactive glial inclusions, including small, round inclusions in oligodendroglia (Fig. 1e) and ramified astrocytes (Fig. 1f) are sometimes present in PiD, but they are not as frequent as in the 4R tauopathies (see below). Interestingly, glial lesions in PiD contain predominantly 4R tau (Hogg et al., 2003), which may contribute to the variability in the ratio between 3R and 4R tau observed in biochemical studies of PiD (Zhukareva et al., 2002). Involvement of deep gray matter and brainstem is common, with a predilection for the monoaminergic nuclei (Yoshimura, 1989). There is overlap between subcortical nuclei affected in PiD compared to both corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Feany et al., 1996).

4R TAUOPATHIES

Corticobasal degeneration

CBD is a 4R tauopathy that has a range of clinical presentations because it is associated with focal cortical degeneration. Factors that determine the distribution of focal cortical degeneration, as in PiD, remains unknown. The classic clinical presentation of CBD, which is referred to as the “corticobasal syndrome (CBS),” is associated with asymmetrical rigidity and apraxia, often with dystonia and alien limb sign (Litvan et al., 2000) and accompanied by asymmetrical cortical degeneration of the superior frontal gyrus and superior parietal lobule. Atypical presentations are common, including presentations similar to bvFTD, with focal atrophy in the frontal lobes (Bergeron et al., 1996) or PNFA with focal degeneration in peri-Sylvian areas (Ikeda et al., 1996). It is increasingly recognized that CBD need not always be asymmetrical (Hassan et al., 2010), and that some of these patients have a clinical presentation indistinguishable from that of PSP (see below) (Ling et al., 2010). It is also clear that the CBS is not specific to CBD, with other pathologies presenting clinically with asymmetrical rigidity and apraxia with dystonia (Boeve et al., 1999, Wadia and Lang, 2007, Ling et al., 2010, Kouri et al., 2011).

The characteristic pathology in CBD is phospho-tau accumulation in cell processes of neurons and glia in the cortex, basal ganglia, thalamus and brainstem (Dickson et al., 2002). The forebrain typically is more affected than the hindbrain, but there are atypical forms of CBD where hindbrain pathology is prominent. The most specific histopathological lesion in CBD is the astrocytic plaque (Feany and Dickson, 1995) (Fig. 2a), which is not seen in other disorders (Komori et al., 1998). Ballooned neurons, also known as swollen achromatic neurons (Rebeiz et al., 1967), similar to those in PiD (Fig. 1d), are usually numerous in affected cortical areas, but they are not specific and can be seen in a number of other disorders (Fujino et al., 2004). Neuronal inclusions in CBS are pleomorphic and often not visible with silver stains due to presence of so-called pretangle-like lesions (Fig. 2c). Neuropathologic research criteria for CBD emphasize the presence of abnormal tau-positive, thread-like processes in both gray and white matter of cortical and subcortical regions, accompanied by variable, sometimes sparse, oligodendroglial inclusions (Fig. 2e). The marked neuritic pathology in both gray and white matter has been validated as diagnostically useful for CBD in one study (Dickson et al., 2002), but not yet independently confirmed.

Progressive supranuclear palsy

Progressive supranuclear palsy affects men and women equally and in most cases presents as an atypical parkinsonism with axial rigidity, postural instability and unexplained falls, with most patients also developing progressive vertical gaze palsy (for which the disorder is named), dysarthria and dysphagia (Steele et al., 1964). The classic clinical presentation is referred to as Richardson syndrome (Williams et al., 2005, Williams et al., 2008) to distinguish it from other clinical variants of PSP and to specify clinical features rather than pathology (i.e. PSP pathology). Other clinical presentations of PSP include bvFTD (Bigio et al., 1999), PNFA or apraxia of speech (AOS) (Josephs et al., 2005), CBS (Tsuboi et al., 2005, Josephs et al., 2006) and pure akinesia with gait failure (PAGF) (Williams et al., 2007, Ahmed et al., 2008). As noted above, some PSP has asymmetric cortical atrophy and can clinically mimic CBS (Boeve et al., 1999, Wadia and Lang, 2007, Ling et al., 2010). In a subset of patients, the clinical features initially are similar to those in Parkinson disease, so-called “PSP-P” (Williams et al., 2005). The distribution of tau pathology determines the particular clinical presentation; some cases have severe brainstem involvement (e.g., PSP-PAGF) and others have severe cortical involvement (e.g., PSP-bvFTD, PSP-CBS and PSP-AOS).

The core neuroanatomical regions affected in all cases of PSP include the basal ganglia, subthalamic nucleus and the substantia nigra (Hauw et al., 1994). Cortical involvement is greatest in motor and premotor cortices (Josephs et al., 2008). Pathology of the cerebellar dentate nucleus and the cerebellar outflow pathway (dentato-rubro-thalamic pathway) is usually severe and associated with profound atrophy of the superior cerebellar peduncle (Tsuboi et al., 2003), which can be used as a biologic marker of disease progression with structural imaging (Nilsson et al., 2007). Atrophy of superior cerebellar peduncle may be mild or absent in atypical cortical presentations of PSP.

The hallmark glial lesion is the tuft-shaped astrocyte (Yamada et al., 1992) or tufted astrocyte (Fig. 2b), while the most characteristic neuronal lesion is the globose neurofibrillary tangle (Fig. 2d). Tufted astrocytes are most abundant in the motor cortex and the corpus striatum. Neuronal loss and gliosis is most marked in the substantia nigra and subthalamic nucleus, where many thread-like processes and oligodendroglial coiled bodies are often found in the thalamic and lenticular fasciculi (Fig. 2f). In PSP threads and coiled bodies are found together, while coiled bodies are less common in thread-rich areas of CBD.

Clinical and pathological overlap in 4R tauopathies

While PiD is biochemically and histopathologically a distinct disorder, almost all available evidence suggests that CBD and PSP form a 4R tauopathy disease spectrum, with clinical presentation driven more by the distribution of the pathology than the histopathologic appearance of the pathology. (The latter is also true for PiD, as noted above.) Typical cases of CBD presenting as CBS and PSP presenting as Richardson syndrome form the extreme ends of the spectrum, but there is considerable overlap in the middle (Fig. 3). As noted above, one of the most common underlying pathologies of CBS is PSP (in some autopsy series being more common than CBD (Ling et al., 2010)). There is also increasing recognition that CBD, especially symmetrical CBD, can present with a clinical syndrome similar to Richardson syndrome (Ling et al., 2010, Kouri et al., 2011). Pathologically, both CBD and PSP are associated with neuronal, oligodendroglial and astrocytic lesions that are immunoreactive for 4R tau. The morphologic features of neuronal and astrocytic lesions and the relative proportion of oligodendroglial lesions (greater in PSP than in CBD) have been used to differentiate PSP and CBD (Komori et al., 1998, Dickson, 1999, Dickson et al., 2010), but the molecular bases of these structural differences is unknown, and there are no specific markers that permit one to differentiate tau pathology in CBD from PSP. Biochemically, both CBD and PSP have increased levels of insoluble 4R tau with few differences noted, except for evidence from a relatively small series of PSP and CBD cases of differential low molecular weight tau fragments, suggesting different proteolytic processes in PSP and CBD (Arai et al., 2004). The biological basis for this difference remains completely unknown. In terms of the little that is known about genetics of CBD and PSP, the evidence suggests that they have a common genetic underpinning. For example, a common genetic risk factor for both PSP and CBD is the *MAPT* H1 haplotype (Baker et al., 1999, Di Maria et al., 2000, Houlden et al., 2001) and the particular subhaplotype, H1c, recognized by the single nucleotide polymorphism, rs242557 (Pittman et al., 2005, Rademakers et al., 2005). More recently, in a genome wide association analysis of pathologically confirmed PSP and CBD, no other gene came close to the association that *MAPT* had for both PSP and CBD (Schellenberg, 2010). It is worth noting that patients with mutations in *MAPT* may have clinical and pathologic features that overlap with both PSP (Stanford et al., 2000) and CBD (Bugiani et al., 1999).

While it will remain important for pathologists to make distinctions between PSP and CBD, since pathology is still the “gold standard” with respect to diagnostic subtyping of FTLT-tau, it is less clear that efforts to distinguish PSP and CBD will pay off in significant clinical benefits. It may be more important to find commonalities between CBD and PSP that can

differentiate them from PiD, a 3R tauopathy, and more importantly from FTLT-TDP, if treatments are developed specific to 4R tau. It will also be important to develop improved methods to differentiate FTLT-tau from FTLT-TDP. Understanding the biologic basis for selective cortical vulnerability is a long-term goal to understand clinical and pathological heterogeneity of FTLT in the primary tauopathies.

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Figure 1. Histopathology of Pick's disease. Pick bodies in dentate fascia with tau immunohistochemistry (a), Bielschowsky silver stain (b), and Gallyas silver stain (c); Ballooned neurons (Pick cell) in cortex with tau immunohistochemistry (d); white matter oligodendroglial inclusions (e); and ramified astrocytes (f). All images, originally ($\times 400$)

Figure 2.

Tau immunohistochemistry in CBD (a, c and e) and PSP (b, d and f). Astrocytic lesions in CBD are referred to as astrocytic plaques (a) due to plaque-like arrangement of cell processes, while in PSP they are called tufted astrocytes (b) because of the tuft like arrangement of cell processes around astrocyte cell bodies. Neuronal lesion in CBD (c) are granular and irregularly dense cytoplasmic deposits consistent with so-called pretangles, while globus neurofibrillary tangles (d) are characteristic of PSP. Oligodendroglial lesions are sparse compared to the dense plexus of thread like structures in white matter of CBD (e), while oligodendroglial coiled bodies (f) are frequent in affected white matter of PSP. All images, originally ($\times 400$)

4R TAUOPATHIES

Figure 3. Clinicopathologic spectrum of the 4R tauopathies. Anatomical distribution of the tau pathology determines the clinical syndrome. (see text for abbreviations)

Table 1

Classification of Most Common Subtypes of FTLT-Tau compared to AD

Disorder	Anatomy (major areas affected in typical cases)	Major clinical feature
4R TAUOPATHIES		
Corticobasal degeneration	Cortex & basal ganglia	Focal cortical syndrome & parkinsonism
Progressive supranuclear palsy	Basal ganglia, brainstem & cerebellum	Atypical parkinsonism
FTDP-17T	Cortex, basal ganglia & brainstem	Focal cortical syndrome & parkinsonism
3R TAUOPATHIES		
Pick's disease	Cortex & limbic lobe	Dementia & focal cortical syndromes
FTDP-17T	Cortex, basal ganglia & brainstem	Dementia & focal cortical syndromes
3R+4R TAUOPATHIES		
Alzheimer disease	Cortex & limbic lobe	Dementia
FTDP-17T	Cortex & limbic lobe	Dementia & psychosis

FTDP-17T = frontotemporal dementia and Parkinsonism linked to chromosome 17, with MAPT mutation and associated with FTLT-tau, to be distinguished from FTDP-17U due to mutations in progranulin gene and associated with ubiquitin-positive, TDP-43 immunoreactive inclusions (Baker et al., 2006)