Chapter 21
The Spectrum of Tau Pathology in Human Prion Disease

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Abstract Intracellular deposition of hyperphosphorylated tau characterizes tauopathies: there is a spectrum from neuron-predominant through mixed neuronal and glial to glia-predominant forms. However, tau pathology appears in practically all forms of human prion disease. In addition to the rare co-occurrence of a main form of tauopathy with prion disease, tau pathology may associate with prion diseases in distinct patterns. (1) Small neuritic profiles correlating with tissue lesioning can be observed in all prion diseases. (2) Larger dystrophic neurites may be observed around PrP amyloid plaques. (3) Neurofibrillary tangles may follow the distribution described by Braak and Braak as Alzheimer-related pathology but might show atypical locations. It may be associated with prominent neuropil threads in subcortical regions in certain mutations with Creutzfeldt–Jakob disease (i.e. E200K mutation). Furthermore, widespread neurofibrillary tangles in several subcortical, allo- and neocortical regions are consistently associated with certain *PRNP* mutations in PrP cerebral amyloidoses such as Gerstmann–Sträussler–Scheinker disease or PrP cerebral amyloid angiopathy. (4) Other types of tau pathologies include the rare presence of glial tau immunoreactivity. In summary, widespread application of phospho-tau immunostaining has revealed a previously underrecognized spectrum of tau pathologies in human prion diseases. The relation between tau pathology and PrP deposition and factors influencing its appearance in prion diseases merit further studies.

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W.-Q. Zou, P. Gambetti (eds.), *Prions and Diseases*,
https://doi.org/10.1007/978-3-031-20565-1_21

Keywords Alzheimer's disease · Argyrophilic grain disease · Cerebral amyloid angiopathy · Corticobasal degeneration · Creutzfeldt–Jakob disease · Dementia with Lewy bodies · Fatal familial insomnia · Gerstmann–Sträussler–Scheinker disease · Glycogen synthase kinase 3β · Neurodegenerative disease · Neurofibrillary tangle · Prion protein · Prion protein gene · Progressive supranuclear palsy · Proteinase K

Abbreviations

AGD	argyrophilic grain disease
AD	Alzheimer's disease
ARTAG	Ageing-related tau astrogliopathy
CAA	cerebral amyloid angiopathy
CBD	corticobasal degeneration
CJD	Creutzfeldt–Jakob disease
sCJD	sporadic CJD
iCJD	iatrogenic CJD
vCJD	variant CJD
gCJD	genetic CJD
DLB	Dementia with Lewy bodies
FFI	Fatal familial insomnia
GSS	Gerstmann–Sträussler–Scheinker disease
GSK3β	glycogen synthase kinase 3β
NDD	Neurodegenerative disease
NFT	neurofibrillary tangle
PART	Primary age-related tauopathy
PD	Parkinson's disease
PK	proteinase K
PrP	prion protein
PRNP	prion protein gene
PSP	progressive supranuclear palsy

21.1 Overview of Tauopathies

Prion diseases belong to the group of neurodegenerative diseases (NDDs) that are characterized by progressive loss of neurons. A prerequisite to understanding the relevance of tau pathology in prion diseases is knowledge of the spectrum of NDDs including tauopathies.

21.1.1 Classification of Neurodegenerative Diseases

Molecular pathological classification of NDDs is based on the regional and cellular sites where the deposits composed of particular proteins are found. While immunoreactivity for amyloid-β or prion protein (PrP) is located predominantly extracellularly, major proteins that deposit intracellularly include tau, α-synuclein, TAR DNA-binding protein 43 (TDP-43) or fused in sarcoma (FUS) protein (Kovacs et al. 2010). Variability in NDDs is reflected by distinctive distributions of neurodegeneration-related proteins that can accumulate in various cell types, i.e. neurons, astrocytes and oligodendroglia, moreover in cell processes, cytoplasm or nucleus. In addition, several biochemical alterations and modifications contribute to the spectrum of phenotypes (Kovacs and Budka 2009b).

21.1.2 Tau Protein

Tau is a microtubule-associated protein encoded by a single gene (*MAPT*). *MAPT* maps to chromosome 17q21.2 (Andreadis et al. 1992; Goedert 2005). Mutations lead to hereditary diseases that associate with progressive neurodegenerative syndromes and accumulation of intracellular deposits of soluble and insoluble hyperphosphorylated tau protein (Goedert 2005; Lee et al. 2001). Genetic variability in *MAPT*, in particular a dinucleotide repeat polymorphism in intron 9 defined as H1 and H2 haplotypes, may contribute to the risk of sporadic tau diseases (Dickson et al. 2007; van Swieten and Spillantini 2007).

Alternative splicing generates six isoforms, which are present in the adult human brain. In disease, four main patterns of insoluble tau are observed on Western blotting (Lee et al. 2001). These include (I) major bands at 60, 64 and 68 kDa (e.g. in AD and primary age-related tauopathy/PART); (II) bands at 64 and 68 kDa (e.g. in corticobasal degeneration/CBD, progressive supranuclear palsy/PSP, argyrophilic grain disease/AGD and globular glial tauopathies/GGT); (III) bands at 60 and 64 kDa (e.g. in Pick's disease); and (IV) a minor band at 72 kDa that usually associates with the first pattern (Kovacs 2015; Lee et al. 2001). It is also important to distinguish different isoforms of tau in diseases. The isoforms differ by the presence or absence of a 29- or 58-amino acid insert in the amino-terminal half of the protein and by the inclusion, or not, of a 31-amino acid repeat encoded by exon 10 of tau in the carboxy-terminal half of the protein. Three isoforms with 0, 1 or 2 inserts contain three microtubule-binding repeats (R) and are designated as 3R tau; and three isoforms, also with 0, 1 or 2 inserts, containing four microtubule-binding repeats, are designated as 4R tau (Goedert et al. 2006).

There are further modifications of the tau protein that are relevant for pathogenesis:

1. The most studied is *phosphorylation*, which is the physiological way of regulating the activity of tau and the microtubule binding (Reynolds et al. 2008). Normal tau is phosphorylated on 2 or 3 residues in contrast to hyperphosphorylated tau that is phosphorylated at least on 8–12 (or more) residues (Kopke et al. 1993).
2. Further modifications are also under extensive investigations but their relevance has to be defined (reviewed in Refs. (Kovacs 2016; Kovacs et al. 2010)). These

include N- and C-terminally truncated species of tau, glycosylation, oxidative and nitrative injuries, transglutamination, deamidation and formation of tau oligomers that may be present before neurofibrillary pathology becomes evident.

21.1.3 Classification of Tau-Related Conditions

Tau-related conditions can be classified on the basis of tau isoforms, 3R, 4R or both 3R and 4R. For clinicopathological classification, the histological and cytological characterization of neuronal and glial tau immunoreactivities and their anatomical distribution is also needed.

While AD features both 3R and 4R isoforms, CBD, PSP and AGD are thought to be 4R predominant, in contrast to Pick's disease, which is a 3R isoform predominant tauopathy (Cairns et al. 2007). Tauopathies associated with mutations in the *MAPT* gene may show any of the patterns and isoform predominance. Thus, tauopathies are currently defined biochemically with a signature characterized by the pattern of insoluble tau and further by the tau isoforms (Sergeant et al. 2005). Recently, high-resolution tau filament structures have been determined, and a three-level hierarchical classification of diseases with tau pathology has been suggested (Shi et al. 2021). Based on the knowledge of aetiology, tau-only pathology versus co-existence with a parenchymal amyloid made of another protein and the role of assembled tau in disease pathogenesis six groups of tau-related conditions have been proposed (Kovacs et al. 2022). Importantly, the terms tau immunoreactivity, tau pathology and tauopathy have been defined. Accordingly, the term tauopathy has been proposed to be used only if the following criteria are met: (1) Abundant filamentous tau inclusions made of either 3R, 4R or 3R+4R tau and (2) consistent and typical patterns of cellular tau pathologies in multiple cases that correlate with clinical signs and neurodegeneration (Kovacs et al. 2022). Main tauopathies include *MAPT*-tauopathies, PSP, CBD, GGT, AGD, PART and Pick's disease; a few examples of 'other' tauopathies include chronic traumatic encephalopathy, IgLON5-antibody-related tauopathy or Western Pacific amyotrophic lateral sclerosis parkinsonism dementia complex (Kovacs et al. 2022).

21.1.4 Immunomorphology of Pathological Tau Deposition in 'Main' and 'Extracellular Filamentous Deposit-RELATED TAUOPAThies'

Hyperphosphorylated tau is the major constituent of neuronal and glial inclusions. Ultrastructurally these are composed of filaments, which may vary in structure, such as paired helical filaments, straight filaments or twisted ribbons. According to the cellular distribution there is a spectrum from neuron-predominant through mixed neuronal and glial to glia-predominant forms of tauopathies (Fig. 21.1a–h)

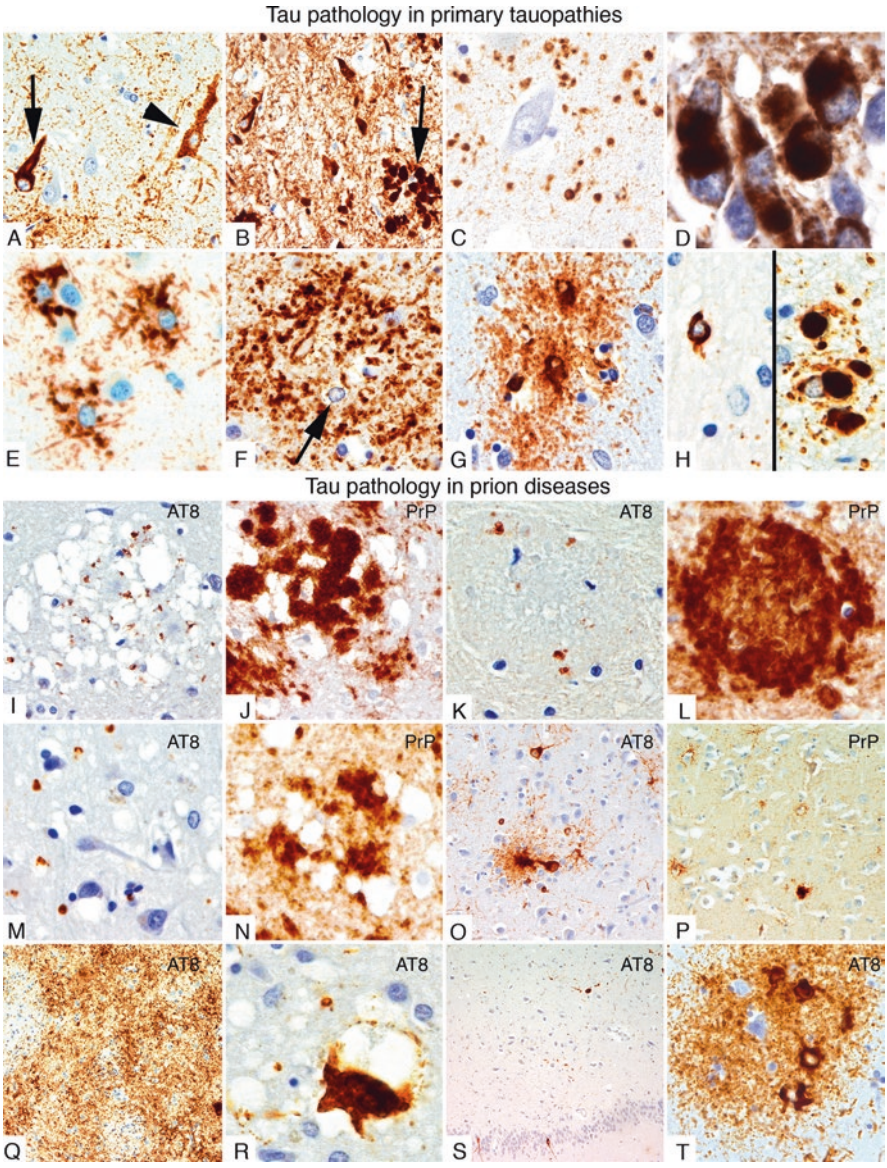

Fig. 21.1 Overview of tau pathology in primary tauopathies and prion diseases. (**a**) Neurofibrillary tangle (indicated by an arrow) and diffuse cytoplasmic neuronal immunoreactivity (indicated by an arrowhead) in Alzheimer's disease hippocampus sample. (**b**) Dystrophic neurites (indicated by and arrow) and neuropil threads in Alzheimer's disease hippocampus sample. (**c**) Grains in the hippocampus in argyrophilic grain disease. (**d**) Pick bodies in the granular layer of the dentate gyrus in Pick's disease. (**e**) Tufted astrocytes in the caudate nucleus in progressive supranuclear palsy. (**f**) Astrocytic plaque in the caudate nucleus in corticobasal degeneration. (**g**) Fine granular/fuzzy tau immunoreactivity in astrocytic processes in complex tauopathy of the elderly. (**h**) Oligodendroglial coiled body (left side of image) and globular glial inclusions (right side of image) in progressive

(Kovacs et al. 2010; Kovacs and Budka 2009b). Neuronal tau pathology predominates in AD and in Pick's disease. These comprise neurofibrillary tangles (NFTs) that are immunoreactive for both 4R and 3R tau isoform-,specific antibodies (e.g. in AD) and spherical inclusions called Pick bodies that are purely 3R isoform immunoreactive (e.g. in Pick's disease). In PSP and CBD, a mixture of neuronal and glial deposition of tau is observed, whereas the anatomical distribution and morphology of cellular inclusions distinguish the disorders. In addition to oligodendroglial coiled bodies seen in both, astrocytic plaques (tau accumulation in the distal segment of astrocytic processes) are features of CBD, and tufted astrocytes (tau deposition in the proximal segment of astrocytic processes) characterize PSP. AGD is a tauopathy where the tau immunoreactive argyrophilic grains and diffuse cytoplasmic granular tau immunoreactivity are neuron-related, but oligodendroglial coiled bodies are also important features, however, restricted to limbic areas. There are further tauopathies where glial tau, in particular in the white matter, is a major feature; these are mainly 4R predominant tauopathies (Bigio et al. 2001; Kovacs et al. 2008b; Powers et al. 2003). Recently, further complex tauopathies associated with dementia in the elderly have been described and expand the spectrum of tauopathies (Kovacs et al. 2011a).

One important feature of some neuronal and astrocytic tau pathologies is the maturation of inclusions. For example, diffuse neuronal cytoplasmic granular tau immunoreactivity cannot be detected using anti-ubiquitin immunohistochemistry; these lesions are not visible either using silver stainings (i.e. Gallyas or Bielschowsky), hence the name 'pretangle'. These are detected using antibodies against the 4R isoform of the tau protein. This morphology is followed by the typical NFT, which is argyrophilic (i.e. detected by silver stains) and ubiquitin immunoreactive (Bancher et al. 1989a; Bancher et al. 1989b). Furthermore, it shows both 3R and 4R tau isoform immunopositivity. A similar process was described also for astroglial tau pathology (Botez et al. 1999; Kovacs et al. 2011a).

To understand the complexity of tauopathies and to interpret tau pathologies, one must be familiar with the fact that some lesions show stages, which means that

Fig. 21.1 (continued) supranuclear palsy and white matter tauopathy with globular glial inclusions, respectively. (**i**) Tau immunoreactive neuritic profiles in the cerebral cortex in variant Creutzfeldt–Jakob disease (CJD). (**j**) PrP immunoreactivity in the corresponding area for image (**i**) (samples of variant CJD were kindly provided by Professor James Ironside, CJD Surveillance Unit, Edinburgh, UK). (**k**) Tau immunoreactive neuritic profiles in the cerebellum in Gerstmann–Sträussler–Scheinker disease (P102L mutation). (**l**) PrP immunoreactivity in the corresponding area for image (**k**). (**m**) Tau immunoreactive neuritic profiles in the cerebral cortex of sporadic CJD. (**n**) Patchy/perivacuolar PrP immunoreactivity in the corresponding area for image (**m**). (**o**) Tau immunoreactive neurons in genetic CJD (E200K mutation). (**p**) Perineuronal and synaptic PrP immunoreactivity in the corresponding area for image (**o**). (**q**) Abundant phospho-tau (AT8) immunoreactive threads in the caudate nucleus in genetic CJD (E200K mutation). (**r**) Globose neurofibrillary tangle with vacuolation in the nucleus accumbens in genetic CJD (E200K mutation). (**s**) Neuronal tau immunopositivity in the granular layer of the dentate gyrus (lower part of image) and the CA4 subregion of the hippocampus (upper part of image) in in genetic CJD (E200K mutation). (**t**) Tau immunopositive astrogliopathy in the amygdala in genetic CJD (V203I mutation)

certain anatomical pathways of the appearance of tau immunoreactive lesions can be recognized. This was originally described for the NFTs seen in AD and has become known as Braak and Braak stages: from the entorhinal cortex and hippocampus and subsequently the temporal cortex, it reaches subcortical structures and association cortices in six stages (Braak and Braak 1991). A similar progressive anatomical involvement has been proposed for PSP (Williams et al. 2007) or AGD (Saito et al. 2004) as well.

21.1.5 Spectrum of Tau Pathology in Other Conditions

Pathological tau may be present in normal aging or non-neurodegenerative disorders (summarized in Refs. (Goedert et al. 2006; Kovacs et al. 2010, 2022; Kovacs and Budka 2009b). In some cases, tau immunoreactivity using various antibodies has been described; however, the presence of filamentous tau inclusions has not been demonstrated (Kovacs et al. 2022). In several conditions, age-associated NFTs are observed. A recently described tau pathology is ageing-related tau astrogliopathy (ARTAG) that includes thorny astrocytes in subpial, subependymal, perivascular, and white matter locations, and granular fuzzy astrocytes in the gray matter (Kovacs et al. 2016).

21.1.6 How Is Tau Pathology in Prion Diseases to Be Characterized?

This requires an analysis of the following aspects:

- Is it within the frame of age-associated neurofibrillary degeneration?
- Is it compatible with a well-established main tauopathy as concomitant pathology, or does it represent a novel phenotype?
- What are the hallmark tau immunomorphologies; in particular, is it neuron or glial predominant, and what is the shape of the inclusions?
- What is the biochemical signature of insoluble tau and what is the ultrastructural feature of filaments?

21.2 Tau Pathology in Human Prion Diseases

Human prion diseases may be classified according to the etiology as idiopathic (sporadic) such as Creutzfeldt–Jakob disease (sCJD), acquired (iatrogenic-iCJD; variant CJD-vCJD), or genetic (familial, hereditary) CJD (gCJD), fatal familial insomnia (FFI), or PrP cerebral amyloidoses such as

Gerstmann–Sträussler–Scheinker disease (GSS) and PrP cerebral amyloid angiopathy (PrP-CAA). These disorders differ in brain pathology: spongiform encephalopathy in CJD, thalamic degeneration in FFI, and brain amyloidosis in the majority of GSS (Kovacs and Budka 2009a). This suggests that additional tau pathology may be influenced by several factors in prion diseases. For long, tau immunohistochemistry was not routinely performed during the neuropathological evaluation of prion diseases; thus, many novel aspects have been described only recently.

21.2.1 Tau Pathology in Sporadic CJD

According to the literature and our experience, a concomitant tau pathology or tauopathy in sCJD may be classified as follows:

1. *Neuritic tau pathology associated with deposition of disease-associated PrP*

This is the most frequent type of tau immunoreactivity. Its presence was underestimated for long, but a study (Reiniger et al. 2011) as well as our experience indicate strong correlation with the density of PrP immunodeposition but not duration of illness. It was proposed that the PrP load is the major triggering factor for tau phosphorylation (Reiniger et al. 2011). The presence of these neuritic profiles was reported to be not related to amyloid-β (Aβ, the protein component of plaques in AD), and the morphological appearance (granular or tiny rod-shaped) was also distinct (Reiniger et al. 2011). Further comprehensive biochemical characterization of tau pathology has not been reported for sCJD. Tau immunoreactivity was described also surrounding kuru-type plaques in a rare sCJD subtype (Sikorska et al. 2009). A recent report suggests that sCJD VV2 and MV2K subtypes show higher levels of p-tau in the cerebrospinal fluid when compared with other sCJD types, and this correlates positively with the amount of tiny neuritic tau pathology (Lattanzio et al. 2017).

2. *Co-existence of AD- and PART-related pathology and CJD*

This is observed in all larger CJD series, as both conditions preferentially occur in the elderly; however, tau pathology and other mixed pathologies (Kovacs et al. 2008a) are thought to be not consistent features of sporadic CJD. A comprehensive study indicated that, according to CERAD (Consortium to establish Registry for AD) criteria (Mirra et al. 1991), definite and probable AD constituted 10.9% of sCJD cases, somewhat lower as in the control group (19%) (Hainfellner et al. 1998). It was concluded that AD-type pathology in CJD is most likely age-related. Two forms of coexistence of CJD and AD in the same patient have been suggested (Tsuchiya et al. 2004): the first when AD patients develop CJD in the late stage of disease, and the second form when sCJD brains show AD pathological features without any clinical features typical of AD. It must be noted that the CERAD approach focuses on the density of neuritic plaques that consist of tau-immunoreactive dystrophic neurites; however, in these studies, other types of tau pathologies were not systematically evaluated using phospho-dependent tau antibodies. In variably

protease-sensitive prionopathy (Gambetti et al. 2008; Zou et al. 2010), NFTs were also reported corresponding to stage II according to Braak and Braak in a 76-year-old patient (Head et al. 2010). A recent study found that approximately 80% of sCJD cases show additional tau pathology in the medial temporal lobe compatible with PART, but in 40% of these, the tau immunoreactivity load was significantly different from the typical distribution of the Braak staging (Kovacs et al. 2017). Complementary to these observations, another study reported a lack of correlation between variables affecting CJD and those defining the AD/PART spectrum and suggested that, except for a tendency to increase the frequency of cognitive symptoms, AD/PART co-pathology did not significantly affect the clinical presentation of typical CJD (Rossi et al. 2019).

3. *Other tau pathologies in sCJD*

These include the rare presence of PSP or CBD-type pathologies and also the presence of AGD and widespread gray matter ARTAG, altogether seen in approximately 14% of sCJD cases (Kovacs et al. 2017).

21.2.2 Tau Pathology in Acquired CJD

Acquired forms comprise prion diseases with suspected or proven exposure to external prions. This includes kuru, related to historical ritualistic cannibalism in Papua-New-Guinea; iatrogenic CJD (iCJD), related to medical intervention (e.g. neurosurgery, deep electrodes, hypophyseal hormones, dura mater transplants); and variant CJD (vCJD), which represents dietary exposure to bovine spongiform encephalopathy (BSE) (Kovacs and Budka 2009a). Although tau-immunoreactivity around plaques has been described in a kuru brain (Sikorska et al. 2009), and Alzheimer-type senile plaques without NFTs have been reported in a single 28-year-old patient with iCJD (Preusser et al. 2006), comprehensive observations on tau pathology have been described only for vCJD: phospho-tau-immunoreactive neuritic profiles clustered around PrP amyloid deposits in vCJD patients in the absence of Aβ, not only in the cerebral cortex but also in the cerebellum (Giaccone et al. 2008). This was localized to perikarya and dendrites less constantly. The biochemical counterpart was the presence of phospho-tau in the detergent-insoluble fraction of cerebral cortex. A further study showed significant tau-immunopositive dystrophic neurites around the PrP-immunoreactive amyloid plaques together with some phospho-tau immunoreactive structures dispersed in the cerebral and, to a lesser degree, the cerebellar cortex (Sikorska et al. 2009). This was considered reminiscent of AD plaques but, in contrast to AD, no paired helical filaments were observed within dystrophic neurites in vCJD on electron microscopy (Sikorska et al. 2009). However, tau pathology seems to be a regular component of the neuropathology of vCJD.

21.2.3 Tau Pathology in Genetic CJD and FFI

Mutations in the *PRNP* associated with spongiform encephalopathy are termed genetic CJD (gCJD). There a tau pathology profile similar to sCJD may be expected and was indeed reported in some mutations (Reiniger et al. 2011). However, a more complex pathogenetic scenario has been suggested in a recent comprehensive evaluation of protein deposition in *E200K gCJD* cases, one of the most frequent *PRNP* mutations worldwide (Kovacs et al. 2011b). Accumulation of phospho-tau, alpha-synuclein, and Aβ was frequent, while TDP-43 immunoreactivity was not present. Moreover, Aβ plaques have been reported in E200K gCJD (Ghoshal et al. 2009). Our previous study on *E200K gCJD* provided the first evidence for a complex interrelation of neurodegeneration-related proteins triggered by a single *PRNP* mutation. Approximately 90% of cases exhibited *neuritic profiles*, mainly in areas with more prominent tissue pathology, PrP deposition, neuronal loss and spongiform change. This finding is consistent with the findings of another study on sCJD and few gCJD cases (Reiniger et al. 2011). Double immunolabeling studies suggested that most of the tau pathology is neuronal in origin (Kovacs et al. 2011b). Immunoblotting revealed bands characteristic of 3R tau. Roughly one-third of the patients showed *NFTs following Braak and Braak stages*. Usually, these were in a more developed stage than what would accord with the age of the patients. Immunoblotting revealed patterns similar to AD in the hippocampus sample, while 3R and fragments of tau were detected in several other regions where only neuritic tau immunopositivity was detected in tissue sections (Kovacs et al. 2011b). A further type of tau pathology, again in about one-third of the patients, comprised a peculiar constellation of tau pathologies that did not fulfill criteria of established sporadic tauopathy entities (Kovacs et al. 2011b). This could be further subdivided into two major types: (A) Cases with NFTs, diffuse cytoplasmic tau immunoreactivity (pretangle-like), and threads in the basal ganglia, brainstem (substantia nigra, dorsal raphe nucleus, and locus coeruelus) and less in the thalamus, including one with prominent involvement of neocortical regions. Globose tangles in subcortical areas were prominently 4R immunoreactive, while in neocortical areas and hippocampus both 3R and 4R immunopositivities were noted in NFTs. Abundant thread-like structures that were associated with neurofilaments, but not astrocytic processes, were mainly 4R immunopositive. There was lack of astrocytic plaques or tufted astrocytes, although some dot-like immunostaining of astrocytic processes was noted. Oligodendroglial coiled bodies were only occasionally seen. (B) Further cases exhibited an unusual distribution of neuronal and glial tau deposition in the hippocampus, which included NFTs and prominent diffuse neuronal granular cytoplasmic immunoreactivity in CA4, CA3 and CA2 subregions and dentate gyrus, but also in the CA1 subregion and subiculum, without or with scant NFTs in the entorhinal cortex. Argyrophilic grains were not seen, but some oligodendroglial tau immunopositivity and dot-like immunolabeling of astrocytic processes were observed. In addition, all of these cases showed NFTs in the noradrenergic locus coeruleus. In these cases, however, further biochemical evaluation of tau protein was not available.

An unusual pattern of tau pathologies was described in the *R208H gCJD* reminiscent of the type B pattern described above in E200K gCJD: few NFTs and neurones with stained cytoplasm (pretangles) in the CA1 region, and a small number of AT8-positive inclusions in oligodendrocytes and astrocytes (Roeber et al. 2005). In addition, tiny granules in the CA1 region and entorhinal cortex were also noted. Since immunoblotting revealed an additional 17-kDa PrP fragment, absent in two other cases with the same R208H mutation but without tau pathology, the possibility that the additional PrP band is related to tau protein pathology was raised (Roeber et al. 2005). Although a similar band was described in *V203I gCJD* recently, findings on tau immunohistochemistry were not reported (Jeong et al. 2010). Interestingly, a single V203I gCJD case in our collection (Höftberger et al. 2011) and a further case from France (Kovacs et al. 2017) exhibited features of an unusual pattern with a peculiar tau-astrogliopathy, originally described in non-prion diseased elderly demented patients (Kovacs et al. 2011a).

NFTs were also reported in *V180I gCJD*. This gene alteration may be present in elderly patients with spongiform encephalopathy; however, NFTs are not consistently reported. In an elderly patient, stage IV of NFTs according to Braak and Braak was noted; however, it was interpreted as similar to sCJD cases having AD pathological features without any clinical features typical of AD (Yoshida et al. 2010).

In *fatal familial insomnia* (FFI), there is also a paucity of systematic studies on tau pathology. However, a recent case report demonstrated neuropil threads and small neuronal inclusions in the anterior ventral and dorsomedial nuclei of the thalamus, the pulvinar, inferior olivary nuclei and striatum together with neuropil threads seen adjacent to the pigmented neurons of the substantia nigra (Jansen et al. 2011a). Distribution of the tau pathology did not follow Braak and Braak staging (Jansen et al. 2011a). This finding is particularly interesting since here PrP deposition is only mild as compared to other prion diseases.

21.2.4 Tau Pathology in Dominantly Inherited PrP Cerebral Amyloidoses

Brain PrP amyloidosis is characterised by the appearance of parenchymal (multicentric) amyloid plaques (GSS) in the brain or in the vessel walls (PrP cerebral amyloid angiopathy, CAA) (Ghetti et al. 1995, 2018). The biochemical hallmark of PrP cerebral amyloidosis is thought to be the presence of N- and C-terminal truncated proteinase K (PK) resistant PrP degradation products that range from approximately 7 to 15 kDa and a low molecular weight band in Western blot (WB) (Ghetti et al. 2003; Piccardo et al. 1998). Hallmark studies from Bernardino Ghetti and coworkers have outlined the complexity of tau pathology (Ghetti et al. 1989, 1995, 1996a, b; Giaccone et al. 1990) that is a very important component of the neuropathology of many cases with cerebral PrP amyloidosis. It is characterized by tau-immunoreactive dystrophic neurites surrounding PrP amyloid plaques and NFTs. However, not all related mutations associate consistently with NFTs.

The following mutations inconsistently show NFTs or other types of tau pathology; such cases tend to have a longer clinical duration:

- P102L-129M: Variably present in hippocampus and cerebral cortex together with neuropil threads, in some cases in correlation with the burden of PrP deposition (Ishizawa et al. 2002).
- P105L-129V: NFTs are present mainly in the cerebral cortex but may appear in the brainstem as well (Yamada et al. 1999; Yamazaki et al. 1999).
- A117V-129V: Described in the cerebral cortex and subcortical nuclei, including amygdala and thalamus with immunobiochemical profile similar to AD (Mohr et al. 1999).
- 168 base pair insertion with 129V: diffuse punctuate phospho-tau staining with sparse neuropil threads in cerebral cortex and also striatum and molecular layer of the cerebellum, but only a few NFTs in the hippocampus, frontal cortex and temporal cortex (Jansen et al. 2011b).

NFTs have been reported also in the following mutations with GSS phenotype: G131V-129M, S132I-129M, H187R-129V, D202N-129V, E211D-129V, Q212P-129M, Y218N-129V, Q227X-129V. NFTs as integral part of the clinicopathological phenotype has been reported in F198S-129V and Q217R-129V mutations with GSS or Y145X-129M, Q160X0129M, or Y163X-129M with PrP-CAA. Neuritic tau-positive dots have been described in Y226X-129V mutation associated with PrP-CAA. Further studies have indicated that the tau immunoreactivity profile and ultrastructure was very similar if not identical to AD (Ghetti et al. 1989, 1996b; Giaccone et al. 1990). The correlation of PrP deposition and tau pathology is reminiscent to that seen in other amyloidoses (Holton et al. 2001) and supports the idea that abnormal tau phosphorylation may accompany cerebral amyloid deposition regardless of the chemical composition of the amyloid. However, this is not always seen in subcortical regions in GSS.

Importantly, tau folds co-existing with various cerebral parenchymal amyloidosis such as PrP amyloid, Abri and ADan amyloid are identical to those of AD (Hallinan et al. 2021; Shi et al. 2021). It has been proposed that the Tauopathy seen in certain *PRNP* mutations associated with PrP amyloidosis should be included in the group of 'Tauopathy, obligatory association with extracellular filamentous deposits caused by genetically determined other proteinopathy' (Kovacs et al. 2022).

21.3 Concluding Remarks

21.3.1 Pathogenesis of Tau Deposition in Human Prion Diseases

The interaction of tau protein and PrP still needs more experimental data. There are a few investigations that provide a pathogenetic link between these two proteins, such as that using PrP 106–126 peptides that induced glycogen synthase kinase 3β

(GSK3β) mediated tau phosphorylation (Perez et al. 2003). A study in scrapie-infected hamsters showed that changes of profiles of phospho-tau correlate with illness (Wang et al. 2010), while gene knockout of tau did not contribute to the pathogenesis of prion disease in mice (Lawson et al. 2011). Since not all mutations with PrP amyloid associate with tau pathology, it might be theoretically possible that binding activities of a PrP–tau complex differ between mutations, as suggested by in vitro observations (Wang et al. 2008). Although there are several components of the tau–PP relation in tissue in parallel with observations in other amyloidoses (Holton et al. 2001), there are many exceptions to the rule. This may suggest differences in neuronal processing or genetic/epigenetic influences. A recent study found no evidence for an association between *MAPT* gene variations and sCJD, and only some weak evidence for an association with vCJD (Sanchez-Juan et al. 2007). Altogether these studies indicate a complex interaction of tau and PrP.

21.3.2 Relevance of Tau Protein as Biomarker in Human Prion Diseases

Examination of total tau and phospho-tau protein levels in the cerebrospinal fluid is an established method used in practice mainly for AD diagnostics. In sCJD, although protein 14-3-3 has traditionally been a most useful surrogate laboratory marker, total tau protein presents comparable levels of sensitivity and specificity (reviewed in Ref. (Quadrio et al. 2011)). Measurement of total tau in the CSF performs best in terms of both specificity and sensitivity for all sCJD types; furthermore, sCJD VV2 and MV2K types demonstrated higher CSF levels of p-tau when compared with other sCJD types (Lattanzio et al. 2017). Interestingly, a high rate of total tau levels was found in gCJD, while in GSS, only 40% of cases had tau levels above the cut-off level, and only a single FFI patient (from 14 investigated) had abnormal tau levels (Ladogana et al. 2009).

21.3.3 Summary: Classification of Tau Pathology in Human Prion Diseases

Tau pathology appears in practically all forms of human prion disease and is mainly neuron-related, while glial tau pathology is unusual. In addition to the rare co-occurrence of main tauopathy with CJD, tau pathology presents in the following patterns (summarized in Figs. 21.1i–t and 21.2):

1. *Small neuritic profiles* correlating with the density of PrP deposition and tissue lesioning. This type can be observed in all prion diseases with spongiform encephalopathy (sCJD and gCJD), but is rare in FFI.

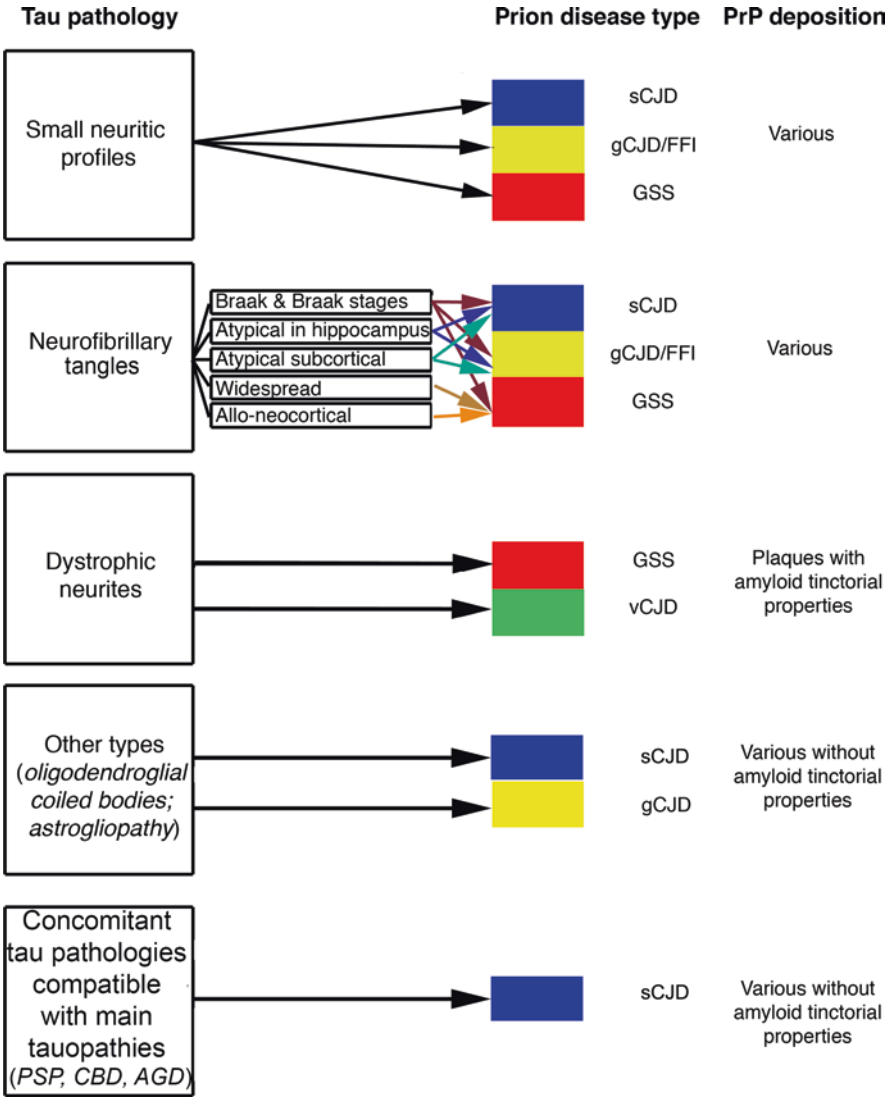

Fig. 21.2 Stratification of tau pathology according to morphology, prion disease type, and PrP immunoreactivity (see text for details)

2. *Larger dystrophic neurites and neuritic profiles* may be observed around multicentric PrP amyloid plaques as a feature of GSS, reminiscent of other brain amyloidoses including AD. Furthermore, it is prominent in the amyloid-plaque predominant vCJD.
3. *NFTs*, which can be further grouped as follows:

   (a) NFTs following the distribution described by Braak and Braak: this might be age-associated but may also appear in more advanced stage in younger patients in gCJD.

(b) NFTs restricted to the medial temporal lobe following or deviating from the Braak and Braak stages, i.e. sparing of the entorhinal cortex with more prominent NFT pathology and diffuse cytoplasmic neuronal immunoreactivity ('pretangles') in the CA4 subregion of the hippocampus or dentate gyrus (i.e. in gCJD).
(c) NFTs and diffuse cytoplasmic neuronal-tau immunoreactivity, together with variably prominent neuropil threads in subcortical regions (basal ganglia and brainstem), associated with PrP deposits lacking amyloid tinctorial properties in gCJD cases (i.e. E200K gCJD or FFI).
(d) Widespread NFTs in several subcortical, allo- and neocortical anatomical regions without predominance in the hippocampus. This is consistently associated with certain *PRNP* mutations associated with brain PrP deposits showing amyloid tinctorial properties (Ghetti et al. 2003); GSS or PrP-CAA phenotype.
(e) NFTs in allocortical and neocortical anatomical regions inconsistently present in certain *PRNP* mutations associated with GSS.

4. *Other types of tau pathologies* include the rare presence of glial tau immunoreactivity either in the form of oligodendroglial coiled bodies (usually restricted to the hippocampus) or tau astrogliopathy.
5. *Concomitant tau pathologies compatible with main tauopathies such as PSP, CBD or AGD.*

21.3.4 Perspectives

Recent widespread application of phospho-tau immunostaining has revealed a previously underrecognized spectrum of tau pathologies in human prion diseases. There are still several issues that merit further studies and clarification:

1. What is the relation between tau pathology and PrP deposition? Is there any evidence of cross-seeding between these two pathogenic proteins? Although small neuritic profiles correlate with the PrP load, the relation of further morphologies with PrP requires more studies (in particular in gCJD).
2. Why is the pattern of hippocampal tau pathology often deviating from the stages of NFTs described by Braak and Braak (1991)?
3. What further factors influence the appearance of tau pathology? In particular (i) why do GSS cases with various mutations, all by definition with prominent amyloidosis, considerably differ with regard to NFTs?; (ii) why does gCJD with the same single mutation (i.e. E200K) associate with a clearly distinct spectrum of tau pathologies, including subcortical and hippocampus predominant forms, while other cases show only small neuritic profiles?; (iii) why do a few cases with sCJD or gCJD show prominent astrocytic tau pathology in the gray matter without other features of main tauopathies?
4. How can the application of biomarkers for tau help to understand better the clinical relevance of concomitant tau pathologies?

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