Chapter 7
The Spectrum of Tau Pathology in Human Prion Disease

Gabor G. Kovacs and Herbert Budka

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 cooccurrence of a primary 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; and (3) neurofibrillary degeneration 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 degeneration in several subcortical, allocortical, and neocortical regions is consistently associated with certain *PRNP* mutations in Gerstmann–Sträussler–Scheinker disease or PrP cerebral amyloid angiopathy. 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.

Keywords Alzheimer 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

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List of Abbreviations

AD	Alzheimer disease
AGD	Argyrophilic grain disease
CAA	Cerebral amyloid angiopathy
CBD	Corticobasal degeneration
CJD	Creutzfeldt–Jakob disease
DLB	Dementia with Lewy bodies
FFI	Fatal familial insomnia
gCJD	Genetic CJD
GSK3β	Glycogen synthase kinase 3β
GSS	Gerstmann–Sträussler–Scheinker disease
iCJD	iatrogenic CJD
NDD	Neurodegenerative disease
NFT	Neurofibrillary tangle
PD	Parkinson's disease
PK	Proteinase K
PRNP	Prion protein gene
PrP	Prion protein
PSP	Progressive supranuclear palsy
sCJD	Sporadic CJD
vCJD	Variant CJD

7.1 Overview of Tauopathies

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

7.1.1 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 protein (FUS) (Kovacs et al. 2010). Variability in NDDs is reflected by distinct distribution 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).

7.1.2 Modifications of Tau Protein

Tau is a microtubule-associated protein encoded by a single gene (*MAPT*). The *Tau* (*MAPT*) gene 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 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. These include (1) major bands at 60, 64, and 68 kDa [e.g., in Alzheimer disease (AD)]; (2) bands at 64 and 68 kDa [e.g., in corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and argyrophilic grain disease (AGD)]; (3) bands at 60 and 64 kDa (e.g., in Pick's disease); and (4) a minor band at 72 kDa that usually associates with the first pattern (Lee et al. 2001). It is also important to distinguish different isofoms 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). 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. In summary, 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).

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 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.

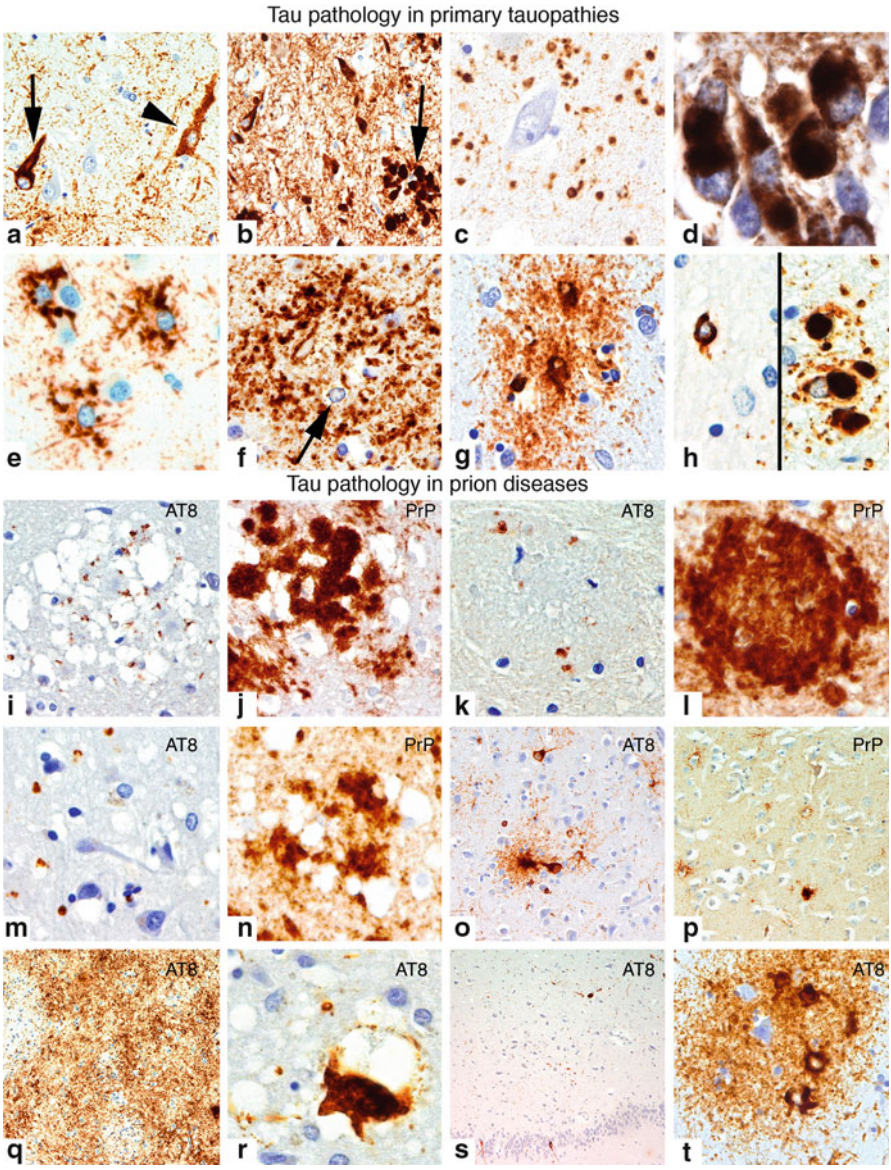

Fig. 7.1 Overview of tau pathology in primary tauopathies and prion diseases. **a**: Neurofibrillary tangle (indicated by an *arrow*) and diffuse cytoplasmic neuronal immunoreactivity (indicated by an *arrowhead*) in Alzheimer's disease hippocampus sample. **b**: Dystrophic neurites (indicated by an *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 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 supranuclear paly and white matter tauopathy with globular glial inclusions, respectively.

7.1.3 *Immunomorphology of Pathological Tau Deposition in Primary 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. 7.1a–h) (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

Fig. 7.1 (continued) **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 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) immu noreactive 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 genetic CJD (E200K mutation). **t**: Tau immunopositive astrogliopathy in the amygdala in genetic CJD (V203I mutation)

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 neurofibrillary tangle, which is argyrophilic (i.e., detected by silver stains) and ubiquitin immunoreactive (Bancher et al. 1989a, b). 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 certain anatomical pathways of the appearance of tau immunoreactive lesions can be recognized. This was originally described for the neurofibrillary degeneration 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.

7.1.4 Spectrum of Tau Pathology in Other Conditions

Pathological tau may be present in normal aging or nonneurodegenerative disorders (summarized in Goedert et al. 2006; Kovacs et al. 2010; Kovacs and Budka 2009b). In several conditions age-associated neurofibrillary degeneration is observed. In dementia with Lewy bodies (LBD), a primary α-synucleinopathy, a wide range of tau pathology may be detected. Chronic traumatic encephalopathy or postencephalitic parkinsonism also represent distinct tauopathies. Tau pathology is known to accompany cerebral amyloidoses or some storage diseases (i.e., Niemann–Pick type C).

7.1.5 How Is Tau Pathology in Prion Diseases to be Characterized?

Association of a tauopathy with other diseases requires analysis of the following aspects:

- Is it within the frame of age-associated neurofibrillary degeneration?
- Is it compatible with a well-established 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?

7.2 Tau Pathology in Human Prion Diseases

Human prion diseases may be classified according to the etiology as idiopathic (sporadic) Creutzfeldt–Jakob disease (sCJD), acquired (iatrogenic CJD—iCJD and variant CJD—vCJD), or genetic (familial and hereditary) CJD (gCJD), fatal familial insomnia (FFI), or Gerstmann–Sträussler–Scheinker disease (GSS). These disorders differ in brain pathology: spongiform encephalopathy in CJD; thalamic degeneration in FFI; and brain amyloidosis in 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.

7.2.1 Tau Pathology in Sporadic CJD

There is a paucity of data on systematic evaluation of phospho-tau immunoreactivity in different anatomical regions in sCJD. In addition to case reports of concomitant AD and sCJD, argyrophilic grains were reported in a single elderly sCJD patient (although not confirmed with phospho-tau immunopositivity) (Kawashima et al. 1999). In our cohort we observed one case combining CBD with sCJD (*unpublished observation*). A recent study evaluated phospho-tau immunostaining in a large cohort of sCJD patients but was restricted to the frontal cortex and cerebellum and focused only on the comparison of tau pathology with PrP immunostaining (Reiniger et al. 2011).

According to the literature and our experience, a concomitant 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 recent study (Reiniger et al. 2011) as well as our experience indicates 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).

2. Coexistence of AD-related and CJD pathology
This is observed in all larger CJD series, as both conditions preferentially occur in the elderly; however, tau pathology as well as 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 than 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 has been suggested (Tsuchiya et al. 2004): the first when AD patients develop CJD in the late stage of disease and a second form when sCJD patients 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), neurofibrillary degeneration was also reported corresponding to stage II according to Braak and Braak in a 76-year-old patient (Head et al. 2010).

7.2.2 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, and 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 neurofibrillary tangles 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 as 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, a tauopathy seems to be a regular component of the neuropathology of vCJD.

7.2.3 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). There accumulation of phospho-tau, α-synuclein, and Aβ was frequent, while TDP-43 immunoreactivity was never present. However, 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 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 *neurofibrillary degeneration 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 features of an *unclassifiable tauopathy* that did not fulfill criteria of established sporadic tauopathy entities (Kovacs et al. 2011b). This could be further subdivided in two major types (a) cases with neurofibrillary tangles, diffuse cytoplasmic tau immunoreactivity (pretangle-like), and threads in the basal ganglia, brainstem (substantia nigra, dorsal raphe nucleus, and locus coeruleus) 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 neurofibrillary tangles. 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 neurofibrillary tangles and prominent diffuse neuronal granular cytoplasmic immunoreactivity not only in CA4, CA3, and CA2 subregions and dentate gyrus, but also in the CA1 subregion and subiculum, without or with scant neurofibrillary degeneration 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 neurofibrillary tangles in the noradrenergic locus coeruleus. In these cases, however, further biochemical evaluation of tau protein was not available.

An unusual pattern of tauopathy was described in the *R208H gCJD* reminiscent of the type B of unusual tauopathy described above in E200K gCJD: few NFTs and neurons 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) exhibited features of an unusual tauopathy associated with a peculiar tau-astrogliopathy described in nonprion diseased elderly demented patients (Kovacs et al. 2011a).

Neurofibrillary degeneration was 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 neurofibrillary degeneration 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 important since here PrP deposition is only mild as compared to other prion diseases.

7.2.4 Tau Pathology in GSS

GSS is a form of brain (PrP) amyloidosis characterized by the appearance of (multicentric) amyloid plaques in the brain (Ghetti et al. 1995). The biochemical hallmark of GSS 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). As atypical cases, at least four stop codon mutations in the *PRNP* feature PrP cerebral amyloid angiopathy (PrP-CAA) (Ghetti et al. 2011). 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 GSS cases. It is characterized by tau-immunoreactive dystrophic neurites surrounding the PrP amlyoid plaques and neurofibrillary degeneration. However, not all GSS mutations are associated consistently with neurofibrillary degeneration.

The following mutations inconsistently show NFTs or other type of tau pathology (those 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 neurofibrillary tangles in the hippocampus, frontal cortex, and temporal cortex (Jansen et al. 2011b).

In contrast, neurofibrillary degeneration has been reported in the following mutations with GSS phenotype: G131V-129M, S132I-129M, H187R-129V, F198S-129V, D202N-129V, Q217R-129V, Y218N-129V, Q227X-129V, furthermore in Y145X-129M, Y160X-129M, and Y226X-129V mutations predominantly 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.

7.3 Concluding Remarks

7.3.1 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 recent 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 differs between mutations, as suggested by recent in vitro observations (Wang et al. 2008). Although there are several components of the tau–PrP 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). All together these studies indicate a complex interaction of tau and PrP.

7.3.2 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 is the best performing surrogate laboratory marker, total tau protein presents comparable levels of sensitivity and specificity (reviewed in Quadrio et al. 2011). Interestingly, a high rate of 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). Although evaluation of phospho-tau in CJD is less helpful, or still needs to be evaluated in all etiological forms of prion disease, an interesting future test seems to be the ratio of total tau to phospho-tau, particularly in the context of evaluating atypical AD patients.

7.3.3 Synopsis: 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 cooccurrence of a primary tauopathy with CJD, tau pathology presents in the following patterns (summarized in Figs. 7.1i–t and 7.2):

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.
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. *Neurofibrillary degeneration*, which can be further grouped as follows:
   (a) Neurofibrillary degeneration 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) Neurofibrillary degeneration restricted to the medial temporal lobe but not following 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).

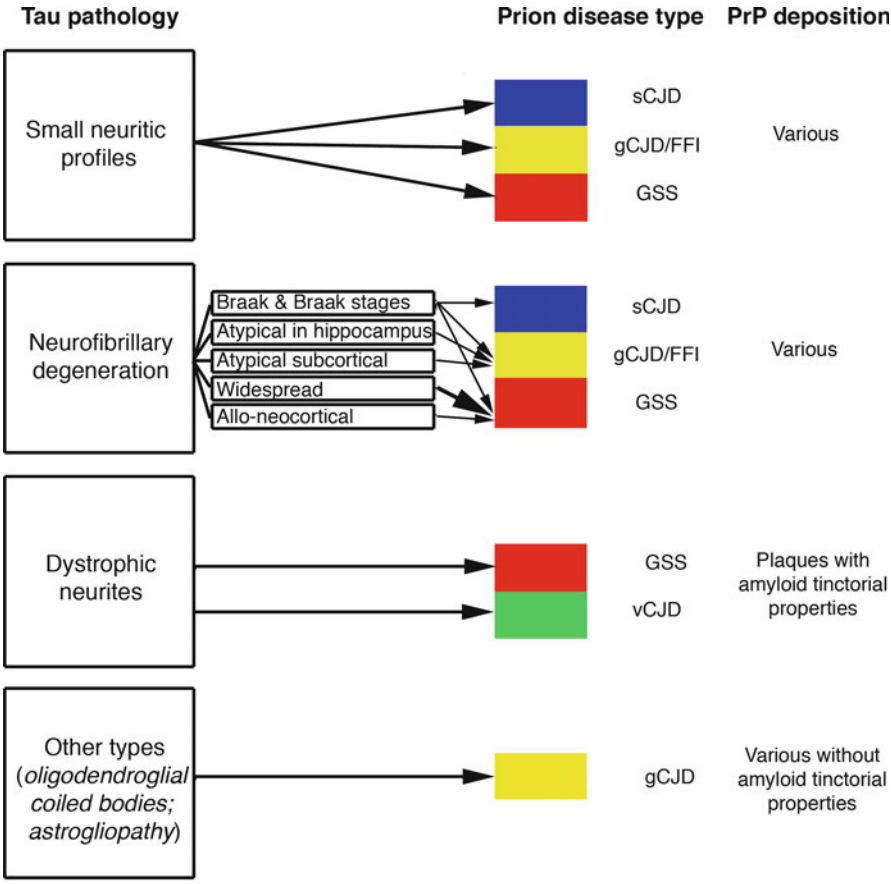

Fig. 7.2 Stratification of tau pathology according to morphology, prion disease type, and PrP immunoreactivity (see text for details)

(c) Neurofibrillary degeneration 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 neurofibrillary degeneration in several subcortical, allocortical, 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) Neurofibrillary tangles 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.

7.3.4 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 full anatomical spectrum of tau pathology in sCJD? Recent studies on a considerable number of cases focused only on the frontal cortex and cerebellum (Reiniger et al. 2011).
2. What is the relation between tau pathology and PrP deposition? Although small neuritic profiles correlate with the PrP load, the relation of further morphologies with PrP requires more studies (in particular in gCJD).
3. What further factors influence the appearance of tau pathology? In particular (1) why do GSS cases with various mutations, all by definition with prominent amyloidosis, considerably differ with regard to neurofibrillary degeneration? and (2) why does gCJD with the same single mutation (i.e., E200K) associate with clearly distinct spectrum of tau pathologies, including subcortical and hippocampus predominant forms, while other cases show only small neuritic profiles?

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