Int J Clin Exp Pathol 2010;3(1):1-23
www.ijcep.com/IJCEP908006

Review Article

Neuropathology of non-Alzheimer degenerative disorders

Dennis W. Dickson

Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA

Received August 23, 2009; accepted August 24, 2009; Available online August 25, 2009

Abstract: Neurodegenerative diseases are characterized by selective and progressive loss of specific populations of neurons, which determines the clinical presentation. The same neuronal populations can be affected in a number of different disorders. Given that the clinical presentation reflects the particular population of neurons that are targets of the disease process, it is clear that for any given clinical syndrome, more than one neurodegenerative disease can account for the clinical syndrome. Because of this clinical ambiguity, for the purpose of this brief review neurodegenerative disorders are classified according to the underlying molecular pathology rather than their clinical presentation. The major neurodegenerative diseases can be classified into amyloidoses, tauopathies, α-synucleinopathies and TDP-43 proteinopathies.

Key words: Amyloidosis, tauopathy, synucleinopathy, TDP-43 proteinopathy

Introduction

By definition a neurodegenerative disease is one in which there is *selective* and *progressive* loss of specific populations of neurons for reasons that in most cases remain unknown. The goals of research on neurodegenerative disorders are to determine the molecular basis of selective vulnerability and common final pathways of progressive neuronal loss. In the most common neurodegenerative disorders there are biochemical changes in a specific protein that often produces characteristic inclusion bodies within neurons or glia, or both. The particular population of neurons that are vulnerable in each disorder determines the clinical presentation, and each specific disorder is defined by a combination of clinical, pathologic and biochemical features. There are genetic underpinnings in most of the common neurodegenerative disorders, but only a small fraction of cases are due to causative mutations in defined genes.

The same neuronal populations can be affected in a number of different disorders. For example, neurons in the hippocampus and brainstem monoaminergic nuclei are vulnerable in a wide range of distinct clinicopathologic entities. Given that the clinical presentation reflects the particular population of neurons that are targets of the disease process, it is clear that for any given clinical syndrome, there will usually be more than one neurodegenerative disease that can account for the clinical syndrome. Because of this ambiguity, for the purpose of this brief review neurodegenerative disorders are classified according to the underlying molecular pathology rather than their clinical presentation.

Molecular classification of neurodegenerative disorders

Table 1 is an abbreviated list of neuro-degenerative disorders classified by the major molecular abnormality, with a greatly simplified listing of anatomical and clinical features.

Amyloidoses

The presence of abnormal proteins with specific properties defines the amyloidoses, of which Alzheimer disease (AD) is the most common. Amyloid is a generic name for proteins with common physicochemical properties (*e.g.*, Congo red birefringence) due to abnormal conformation, with cross beta-pleated sheets, which gives the

Table 1. Classification of major neurodegenerative disorders

	Disorder	Anatomy	Major clinical feature
Amyloidoses			
Aβ	Alzheimer disease	Corticolimbic	Dementia
ABri	Familial British dementia	Corticolimbic & cerebellar	Dementia & ataxia
PrP	Creutzfeldt-Jakob disease	Cortical & basal ganglia	Dementia & movement disorder
	Gerstmann-Straussler-Scheinker	Cortical & Cerebellar	Ataxia & dementia
Tauopathies			
4R	Progressive supranuclear palsy	Basal ganglia & brainstem	Parkinsonism
	Corticobasal degeneration	Cortical & basal ganglia	Focal cortical syndrome & parkinsonism
	Argyrophilic grain disease	Limbic	Amnestic cognitive impairment
3R	Pick's disease	Corticolimbic	Dementia & focal cortical syndromes
3R+4R	Tangle predominant dementia	Limbic	Dementia
	Guam Parkinson dementia complex	Cortex & brainstem	Dementia & parkinsonism
Synucleinopathies			
	Parkinson disease	Brainstem	Parkinsonism
	Dementia with Lewy bodies	Corticolimbic & brainstem	Dementia & parkinsonism
	Multiple system atrophy	Basal ganglia, brainstem & cerebellum	Parkinsonism & ataxia
TDP-43 proteinopathies			
	Amyotrophic lateral sclerosis	Motor neurons	Spasticity & weakness
	Frontotemporal lobar degeneration with ubiquitinated inclusions	Cortex & basal ganglia	Dementia & focal cortical syndromes

protein a propensity to form fibrils and to aggregate, most often as extracellular deposits. The amyloidoses are sometimes referred to as beta-fibrilloses to reflect this molecular property [1, 2]. The amyloid protein in AD, Aβ, is derived from a precursor protein, amyloid precursor protein (APP) by regulated intramembranous proteolysis [3]. By most accounts this process is considered to be fundamental to the pathogenesis of AD [4]. Deposits of Aβ are not found only in AD, but also in elderly nondemented individuals [5], sometimes in great numbers in a process we call pathological aging [6]. Recently, it has become possible to detect Aβ deposits in the brains of living subjects with positron emission tomography, and these studies have also shown that a significant number of clinically normal elderly individuals have Aβ deposits [7, 8]. Whether this represents preclinical AD remains to be determined. Deposits of Aβ are also found in other neurodegenerative disorders, as a function of age and apolipoprotein E ε4 carrier state [9], which is the major genetic risk factor for AD [10]. Amyloid plaques are often abundant in dementia with Lewy bodies (DLB) [11].

Amyloid of a different molecular nature accumulates in a rare form of dementia originally

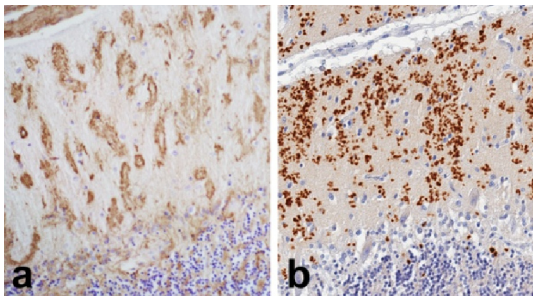

Figure 1. Amyloidoses: Familial British dementia (a) and familial Creutzfeldt-Jakob disease (b) have cerebellar amyloid deposits composed on non-Aβ amyloid, ABri and PrP.

described in British families [12]. The mutation in familial British dementia (FBD) introduces a stop codon in the normal protein, ABri, creating a truncated protein with amyloidogenic properties. Amyloid deposits in FBD are in blood vessels and adjacent tissue and are numerous in cortex and cerebellum (**Figure 1**). Like AD, FBD is associated with neurofibrillary tangles composed of tau protein (see below), but unlike AD tangles are relatively restricted to the medial temporal lobe, while they are widespread in the cortex in AD [13].

Another rare form of non-Alzheimer degenerative dementia associated with non-Aβ amyloid deposits is Creutzfeldt-Jacob disease (CJD). The protein deposited in tissue is an abnormal conformer of a normal cellular protein, PrP, referred to as PrP^{res} [14], reflecting the fact that the abnormal protein is resistant to proteolytic degradation. Amyloid deposits composed of PrP^{res} are particularly common in familial variants of CJD with insertion mutations in the prion gene (*PRNP*) [15] and in Gerstmann-Straussler-Scheinker syndrome (GSS) [16], but are also found as dense kuru-like plaques in sporadic CJD. The latter term reflects the fact that similar amyloid plaques are detected in kuru, a form of transmissible prion disease associated with ritualistic cannibalism in the Fore population of Papua New Guinea [17]. Sporadic CJD is classified based upon the nature of the electrophoretic mobility of PrP^{res} and the genotype at codon 129 of *PRNP* [18]. Kuru-type plaques are most common in cases with heterozygosity at codon 129 (M/V) and type 2 PrP^{res} [18]. Amyloid plaques, in particular multicentric plaques with peri-plaque vacuolation ("florid plaques") are a characteristic feature of variant CJD, which is linked to bovine spongiform encephalopathy [19, 20].

Like FBD, some cases of GSS are associated with neurofibrillary tangles similar to those in AD [21, 22]. Given the widespread distribution of amyloid plaques and neurofibrillary tangles, such cases can be mistaken for an unusual variant of AD [23]. The presence of neurofibrillary pathology in amyloidoses due to distinct molecular forms of amyloid (Aβ, ABri and PrP^{res}) is a strong argument that in these disorders, neurofibrillary pathology is being driven by factors directly related to the amyloid formation and can be considered "secondary tauopathies."

Tauopathies

The major structural protein of neurofibrillary tangles is the microtubule associated protein, tau [24]. Tau is a heat-resistant phospho-protein that promotes microtubule polymerization and stabilization. Once considered to be relatively restricted to neurons [25], 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. That tau pathology is fundamentally important has been proven unequivocally since mutations in the gene for tau (*MAPT*) cause neurodegeneration in humans [26] and in transgenic animal models over expressing mutant tau [27].

Disorders in which tau pathology is considered to be 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. In neurodegenera-tive diseases tau protein has an abnormal conformation and abnormal solubility properties that favor its aggregation and fibril formation, similar to amyloid, except that the fibrils are not in the extracellular space, but within the cytoplasm of the affected cells. Exon 10 of *MAPT* is alternatively spliced to generate tau species with either three or four conserved ~30 amino acid repeats in the microtubule binding domain of tau protein [28], referred to as 3R and 4R tau. There is preferential accumulation of 3R or 4R tau in various tauopathies, providing an additional subclassification of the tauopathies. In AD neurofibrillary pathology is composed of an equimolar ratio of 3R and 4R tau [29].

Argyrophilic grain disease (AGD)

The most common of the primary tauopathies are 4R tauopathies, and all disorders of this type are associated with both neuronal and glial tau inclusions. The most common of these is argyrophilic grain disease (AGD), which increases in frequency with age and is detected in about 5% of autopsies of individuals with late onset dementia [30, 31]. It is common in mild cognitive impairment [32], and it may co-exist with other degenerative disorders, particularly the 4R tauopathies, such as corticobasal degenera-tion (CBD) and progressive supranuclear palsy (PSP) [33].

The characteristic lesion in AGD is the comma shaped or grain-like structure in the neuropil of the medial temporal lobe [34]. Grains are aggregates of tau in dendritic processes of neurons [35]. Neuronal tau is accompanied by tau-positive oligodendroglia ("coiled bodies" [36]) and ramified astrocytes [37]. Ballooned neurons are also common [38]. Many cases of AGD have varying degrees of Alzheimer type neurofibrillary degeneration, and it can be difficult to detect AGD in cases with severe Alzheimer type pathology [34]. Use of immunohistochemistry with an antibody specific for 4R tau [30] permits detection of AGD even in advanced AD, since grains and glial lesions are selectively labeled [39] (**Figure 2a and b**). Using this technique demonstrates AGD in more than 25% of AD cases, with increasing frequency with increased age.

Clinicopathologic correlations in AGD are challenging due in part to the fact that it is rarely a pure pathologic process, and since it is most common in the very old where other pathologic processes increase in frequency with advancing age [40]. The predilection of this pathology to the medial temporal lobe would suggest that an amnestic clinical syndrome should be common in AGD, and in patients with amnestic mild cognitive impairment who come to autopsy, AGD is sometimes found [41]. Saito and co-workers have suggested a staging scheme for AGD, with extension to other limbic related structures in advanced stages of the disease; rarely AGD spreads beyond limbic lobe structures, so-called "diffuse AGD," in patients with dementia [42].

Corticobasal degeneration (CBD)

CBD is a 4R tauopathy that has a range of clinical presentations due to the fact that it is associated with focal cortical degeneration, the distribution of which varies from person to person for reasons that still remain to be explained. In the classical presentation, which is referred to as the "corticobasal syndrome (CBS)," there is asymmetrical cortical degeneration of the superior frontal gyrus and superior parietal lobule and the patient has asymmetrical rigidity and apraxia, often with dystonia and alien limb sign [43]. More often there is focal atrophy of the frontal lobes producing frontal lobe dementia or of language areas producing progressive nonfluent aphasia [44]. The characteristic pathology is phospho-tau accumulation in cell processes of neurons and astrocytes in the cortex, basal ganglia, thalamus and brainstem [45]. The most specific lesion in the neuropathologic diagnosis of CBD is the astrocytic plaque [46] (**Figure 2c**), which is not seen in other disorders [47]. Ballooned neurons, also known as swollen achromatic neurons [48] (**Figure 2c, inset**), are usually numerous in affected cortical areas. On the other hand, research criteria for CBD emphasize presence of abnormal tau-positive, thread-like processes in both gray and white matter of cortical and subcortical regions (**Figure 2d**) , a feature that has been validated as diagnostically useful [45].

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy 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 [49]. Other clinical presentations are also recognized, including dementia [50], speech apraxia [51], corticobasal syndrome [52] and pure akinesia with gait failure [53, 54]. In a subset of patients the clinical features initially are similar to those in Parkinson disease, so-called "PSP-P" [55]. The distribution of tau pathology determines the particular clinical presentation; some cases have severe brainstem involvement (*e.g.*, pure akinesia) and others have severe cortical involvement *(e.g.*, dementia, corticobasal syndrome [56] and speech apraxia).

The core neuroanatomical regions affected in all cases of PSP include the basal ganglia, subthalamic nucleus and the substantia nigra [57]. Pathology of the cerebellar dentate nucleus and the outflow pathway (dentato-rubro-thalamic pathway) is usually severe and associated

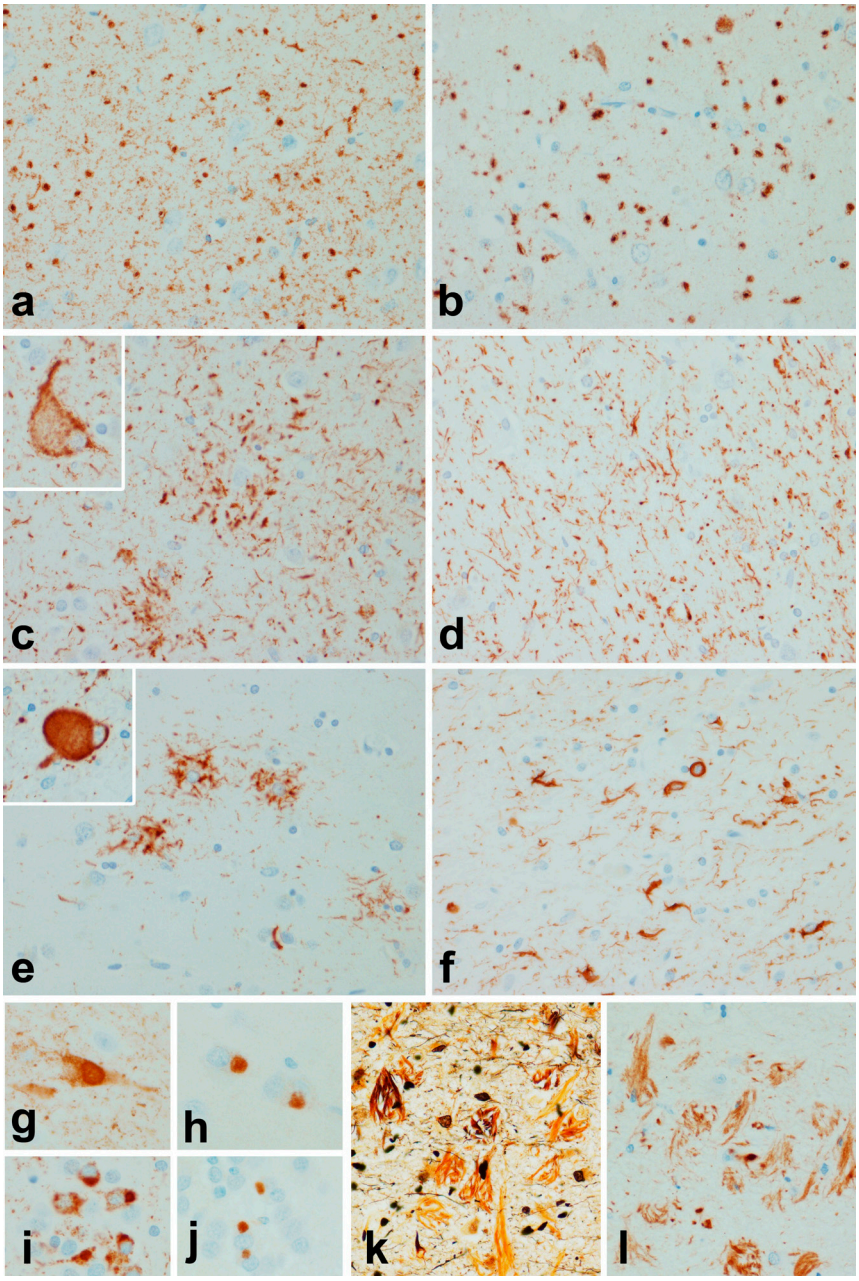

Figure 2. Tauopathies: a & b Argyrophilic grain disease (AGD); c & d Corticobasal degeneration (CBD); e & f Progressive supranuclear palsy (PSP); g-j Pick's disease (PiD); k & l Guam Parkinson dementia complex (PDC). The neuropil of AGD has small round inclusions in neuronal processes (a) that are composed of 4R tau as shown with a monoclonal antibody specific to 4R tau (b). The histologic hallmarks of CBD are astrocytic plaques, which appears as a cluster of short tau positive processes around a central astrocyte (c), ballooned neurons (inset) and thread-like processes in both gray and white matter (d). In PSP the characteristic astrocytic lesion appears as a tuft of abnormal fibers (3), globose neurofibrillary tangles (inset) are the typical neuronal lesion and oligodendroglia in white matter have inclusions referred to as "coiled bodies (f). The defining histologic lesion in PiD is the Pick bodies shown with phospho-tau immunohistochemistry in pyramidal neurons of the hippocampus (g) and granular neurons of the dentate gyrus (i). The inclusions are composed to 3R tau as demonstrated with a monoclonal antibody to 3R tau (h and j). In Guam PDC there are numerous neurofibrillary tangles in cortex and hippocampus (k & l) with many of the tangles released into the extracellular compartment after neuronal death (Bielschowsky stain in k). The tangles are positive for 3R and 4R tau, but extracellular tangles show preferential immunoreactivity for 3R tau (l).

with profound atrophy of the superior cerebellar peduncle [58], which can be used as a biologic marker of disease progression with structural imaging [59].

The hallmark neuronal lesion is the globose neurofibrillary tangle (**Figure 2e, inset**), while tuft-shaped astrocytes or tufted astrocytes (**Figure 2e**) are the most characteristic glial lesion in PSP [60]. 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 (**Figure 2f**). In PSP threads and coiled bodies are found together, while in CBD many threads are detected in the near complete absence of coiled bodies (compare **Figure 2d and 2f**).

Pick's disease (PiD)

PiD is a rare cause of frontal lobe dementia, accounting for less than 5% in autopsy series of dementia [61]. It is associated with circumscribed "lobar" atrophy; like CBD the distribution of focal cortical degeneration determines the presentation. Behavioral and personality deterioration deficits are typical in cases with frontotemporal atrophy, while frontoparietal atrophy presents with apraxia or aphasia similar to CBD. When the amnestic symptoms prevail the clinical diagnosis is often initially AD. It is a disorder that affects men and women equally and is usually a "presenile dementia" with age of onset younger than 65 years. Mutations in the tau gene (*MAPT*) account for most cases of pathologically confirmed cases of familial PiD [62, 63].

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 (**Figure 2g and i**). Pick bodies are composed of tau protein enriched in 3R tau, which can be shown with biochemical studies [64], or more recently with antibodies specific to tau isoforms [65] (**Figure 2h and j**). Less specific features include leukoencephalopathy and ballooned cortical neurons (Pick cells), which are similar to those found in CBD. Glial reaction is often pronounced in affected cerebral gray and white matter. Tau-immunoreactive glial inclusions are sometimes present in PiD [63]. Interestingly, the glial lesions contain predominantly 4R tau, which may contribute to the variability in the ratio between 3R and 4R tau observed in some cases of Pick's disease [66]. Involvement of the deep gray matter and the brainstem is typical, with a predilection for the monoaminergic nuclei [67]. Neuro-chemical studies demonstrate deficits in intrinsic cortical neurotransmitter systems (e.g., somatostatin), but usually less involvement of transmitters in systems projecting to the cortex, such as the cholinergic neurons of the basal nucleus of Meynert [68].

Tangle predominant dementia

Tangle predominant dementia is a disorder of the very old (80 years and greater), where it may account for more than 5% of dementia cases [69-73]. It is associated with predominantly an amnestic clinical syndrome and can sometimes be differentiated from AD because of this [70], although it still remains an entity that is better known to neuro-pathologists than to clinicians. Unlike AD, it is not associated with increased frequency of apolipoprotein E ε4 allele [71-73].

Pathologically, it is characterized by diffuse cerebral atrophy with the most severe atrophy in the medial temporal lobe, which corresponds to the distribution of neuro-fibrillary tangles. Tangles are most dense in the hippocampus, amygdala and medial temporal cortex, with fewer in convexity cortices. There are usually no or very few neocortical neuritic plaques, but there may be diffuse amyloid deposits [74], which are diagnostically nonspecific, since they can be found in large numbers in the brains of neurologically normal elderly individuals (*i.e.* pathological aging) as mentioned previously [6]. The tangles are histologically and biochemically similar to those in AD, with an admixture of 3R and 4R tau [69] (**Figure 2k & l**). Many of the tangles are extracellular "ghost" tangles. For reasons that remain unclear extracellular tangles preferentially are immunoreactive for 3R tau (**Figure 2l**), while intracellular tangles have a mixture of 3R and 4R tau [69].

Guam Parkinson dementia complex (PDC)

Guam PDC is an endemic disease affecting the Chamorro people of Guam characterized by progressive dementia and parkinsonism first

described by Hirano and colleagues [75, 76]. A similar disorder occurs in the Kii peninsula in Japan [77]. In both populations, the disorder clusters in families and there is also increased frequency of motor neuron disease. The etiology is unknown and despite more than three decades of research, a genetic cause is unknown [78].

Pathologically, Guam PDC is characterized by diffuse cerebral atrophy with degeneration of brainstem monoaminergic nuclei. In areas of cortical and subcortical degeneration, neurons have tangles similar to those in AD [79], with 3R and 4R tau. Some cases have Lewy bodies [80], but they are usually restricted to the amygdala, as is common in AD [81]. Recently, TAR DNA binding protein of 43 kDa (TDP-43) has been shown to be present in most cases of Guam PDC [82, 83]. In cases with motor neuron disease, the TDP-43 pathology resembles than seen in sporadic amyotrophic lateral sclerosis (see below), but in PDC cases lacking motor neuron pathology TDP-43 pathology is present in cortical and subcortical areas in the form neuronal cytoplasmic inclusions, dystrophic neurites and oligodendroglia inclusions [83].

Synucleinopathies

Alpha-synuclein is a member of a family of proteins that also contains β-synuclein and γ-synuclein that are pleiotropic in terms of function [84]. In the central nervous system α-synuclein has been implicated in several disorders. It was originally discovered as a non-amyloid component of senile plaques that was enriched in presynaptic termini [85, 86], but little attention was paid to it until mutations were discovered in the gene for α-synuclein (*SNCA*) in familial Parkinson disease (PD) [87] and it was found to be the major structural protein in Lewy bodies, the hallmark histopathologic lesion in PD and dementia with Lewy bodies (DLB) [88]. Availability of antibodies to α-synuclein proved essential to the greater recognition of the importance of Lewy body disorders and the presence of α-synuclein in other neurodegenerative disorders, the synucleinopathies, which includes multiple system atrophy and neuroaxonal dystrophies.

Lewy body disorders

As noted above, Lewy bodies are the histologic hallmark of PD, but they are found in other disorders, as well, including as many as 10% of neurologically normal elderly over age 60 years, where they are considered coincidental [89]. They are the *sine qua non* of DLB and have been noted in a subset of other neurodegenerative disorders, such as AGD, PSP, CBD and PiD [90]. In these disorders they are considered to be coincidental [91]. Lewy bodies are also common in AD, particularly in the amygdala [81, 92], where up to 50% of AD cases are positive [93]. Lewy bodies and α-synuclein immunoreactive axonal spheroids have been described in some of the neuroaxonal dystrophies, particularly neurodegeneration with brain iron, formerly known as Hallervorden-Spatz disease [94, 95].

PD is a disorder characterized by bradykinesia, tremor and rigidity with gait and balance disorders. Motor deficits in PD are associated with loss of substantia nigra dopaminergic neurons [96]. Much current interest in PD is focused on non-motor aspects of the illness, such as hyposmia, autonomic dysfunction and sleep disorders that may precede motor problems by decades [97-99], as well as on cognitive deficits that occur late in the disease course in about 40% of cases [100]. Braak and co-workers have proposed a staging scheme for PD in which early pathology is in peripheral autonomic nervous system, with later involvement of the olfactory bulb and the lower brainstem autonomic and sleep related nuclei, spreading in a caudal-to-rostral manner, ending with widespread cortical involvement [101]. This scheme fits with premotor aspects of PD and late developing dementia in PD [101-103]. The scheme posits a direct cell-to-cell transmission of a causative agent to account for the interrelation of vulnerable neuronal populations. Recently, *in vitro* studies have provided support for the notion that abnormal conformers of α-synuclein can be transmitted from cell-to-cell [104], which may explain the intriguing observation that Lewy bodies are found in engrafted tissue many years after fetal tissue transplants for treatment of PD [105, 106]. The results suggest that α-synuclein may have properties similar to other transmissible amyloid proteins, such as prion protein [107].

The Lewy body is a concentric hyaline perikaryal inclusion (**Figure 3a**) that is immunereactive for α-synuclein, but similar inclusions are also present in neuronal cell processes as so-called intraneuritic Lewy bodies. Less well defined inclusions, so-called cortical Lewy bodies are

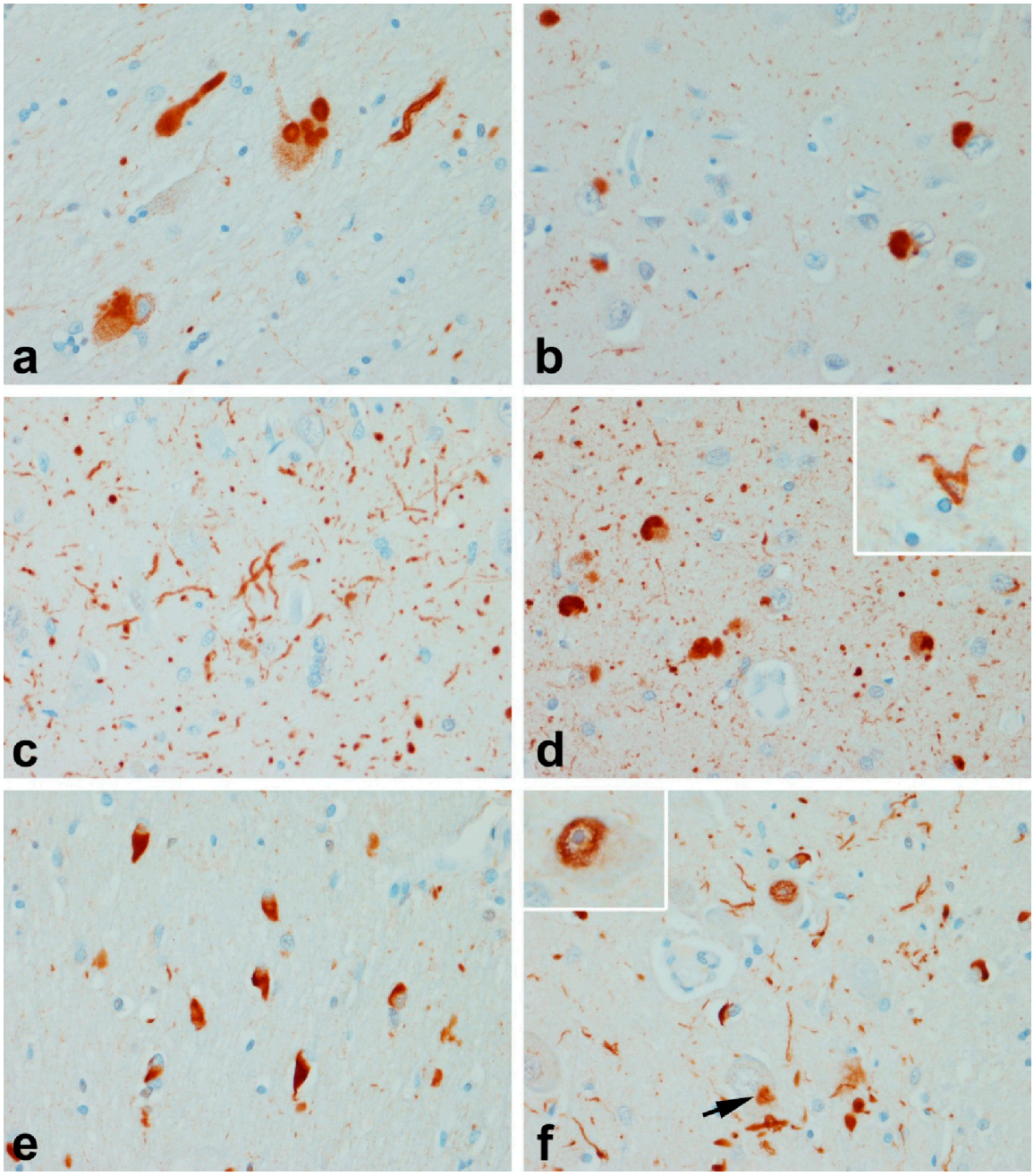

Figure 3. Synucleinopathies: a-d Lewy body disease (LBD); e & f Multiple system atrophy (MSA). Vulnerable neurons in LBD, such as the basal nucleus of Meynert (a) have dense round inclusions (Lewy bodies) as well as Lewy bodies with axons (a). In cases with dementia, there are also neuronal inclusions in cortical neurons (b), as well as many neurites in the hippocampus (c) and amygdala (d). The morphology of the neurites in the amygdala are often grain-like and have been referred to as Lewy dots to distinguish them from argyrophilic grains. In some cases there are sparse oligodendroglial inclusions (inset in d), which are clearly different from the glial cytoplasmic inclusions (GCI) that are the hallmark of MSA (e). GCI are abundant in the basal ganglia, pons (e), medulla and cerebellum. In addition to GCI neuronal inclusions (arrow in f) are present in many cases and are usually most numerous in the pontine base (f) where they are accompanied by dystrophic neurites and synuclein positive fibrillar inclusions within some neuronal nuclei (inset).

found in the cortex in PD with dementia (PDD) and in DLB (**Figure 3b**). DLB is a disorder characterized by dementia with visual hallucinations, fluctua-tions and parkinsonism [108, 109]. It is distinguished from PDD by the temporal sequence of cognitive impairment with respect to parkinsonism, being early in DLB and late in PDD [110]. Pathologically, most cases of rigorously diagnosed DLB have diffuse cortical Lewy bodies with mild Alzheimer type pathology (Braak stage IV or less with mostly diffuse type amyloid plaques) [111].

The largest burden of abnormal α-synuclein in DLB, as well as in PD and PDD, is not in Lewy bodies, but rather dystrophic neurites, so-called Lewy neurites. Lewy neurites are curvilinear or dot-like processes [112] that are found in regions with the highest density of Lewy bodies, such as limbic cortex and amygdala (**Figure 3d**). They are also found in most cases of PDD and DLB in the CA2/3 sector of the hippocampus [113, 114] (**Figure 3c**). The density of cortical Lewy bodies and neurites correlates with cognitive impairment in some studies [115-118]. On the other hand, some studies fail to find a clear correlation [119-121]. In many cases of PD, α-synuclein is also present in small glial cells consistent with oligodendroglia (**Figure 3d, inset**); these can be particularly numerous in early onset PD due to mutations in *SNCA* [122]. The glial lesions in PD and DLB are never as numerous as in multiple system atrophy (MSA).

Multiple system atrophy (MSA)

MSA is a sporadic synucleinopathy characterized by autonomic dysfunction, parkin-sonism and cerebellar ataxia, associated with neurodegeneration of the substantia nigra, basal ganglia, pontine nuclei, inferior olivary nucleus and the cerebellum [123]. Depending upon the prevailing clinical features, it is sub-classified as MSA-P (for parkinsonism) and MSA-C (for cerebellar ataxia). While it is usually sporadic, there are recent reports suggesting that variants in *SNCA* may be associated with increased risk for MSA [124].

Neurodegeneration in MSA is associated with extensive α-synuclein pathology in oligodendrocytes, so-called glial cytoplasmic inclusions (GCI) [125] (**Figure 3e**). How glial pathology is linked to neuronal loss remains to be determined. Neuronal inclusions and dystrophic neurites (**Figure 3d**) are detected in most cases, but they are highly variable in density, not clearly associated with neuronal loss and largely confined to the putamen, pontine nuclei and inferior olive. In some cases there are α-synuclein immunoreactive intranuclear inclusions [126] (**Figure 3d, inset**).

TDP-43 proteinopathies

Transactive response DNA binding protein of 43 kDa (TDP-43) has structural properties similar to heterogenous nuclear ribonucleo-proteins, including RNA binding domains, which appear necessary in its role in transcriptional regulation [127]. More recently, TDP-43 has been shown to be a component of RNA granules [128], which play a critical role in cellular response to cell stress by arresting translation [129]. Interest in TDP-43 grew when it was shown to be a component of the neuronal inclusions of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U) [130]. While initially considered specific to ALS and FTLD-U, it has become clear that TDP-43 immunoreactive neuronal inclusions are found in other disorders, such as AD and hippocampal sclerosis [131], Guam PDC [82] and LBD [132].

Amyotrophic lateral sclerosis (ALS)

ALS is a neurodegenerative disease process known for its selective involvement of upper and lower motor neurons, but increasingly it is has been shown to be a multisystem degeneration with pathology in extra-motor locations [133]. As is true for most neurodegenerative diseases, a small subset of ALS is due to genetic mutations. Autosomal dominant forms of ALS are due to mutations in superoxide dismutase 1 (*SOD1*) [134], angiogenic (*ANG*) [135] and *TARDBP*, the gene for TDP-43 on chromosome 1 [136]. Recently, mutations in *TARDBP* have been reported in a family with frontotemporal dementia [137], but most mutations in *TARDBP* are associated with ALS.

In addition to neuronal loss, affected neurons in ALS have characteristic inclusions bodies, including Bunina bodies, Lewy-like hyaline inclusions and skein-like inclusions [133]. Bunina bodies are eosinophilic granular cytoplasmic inclusions that are found in degenerating motor

neurons and are immune-reactive for cystatin C [138]. The hyaline neuronal and glial inclusions in *SOD1*-linked familial ALS are immunoreactive for SOD1, but not TDP-43 [139]. In contrast, Lewy-like hyaline inclusions and skein-like inclusions in ALS are TDP-43-positive (**Figure 4**).

Frontotemporal lobar degeneration with ubiquitin inclusions (FTLD-U)

Frontotemporal lobar degeneration (FTLD) is a generic term for the group of non-Alzheimer degenerative dementias with focal cortical pathology in frontal and temporal lobes [140]. It encompasses a range of different clinical syndromes – behavioral variant fronto-temporal dementia (FTDbv), progressive nonfluent aphasia (PNFA), semantic dementia (SD) and corticobasal syndrome (CBS) – and a range of different pathologies. The most common is FTLD-U, with tauopathies considered slightly less common and including PSP, CBD and PiD [141]. Mutations in *MAPT* account for a subset of the familial FTLD, all of which are associated with tauopathies (FTLD-TAU) [26]. Mutations in the gene for progranulin (*GRN*) account for most of the cases of familial FTLD-U [142]. A rare cause of familial FTLD-U is mutation in valosin containing protein (*VCP*), which produces dementia with Paget's disease of bone and inclusion body myositis (IBM) [143]. In this disorder there are also TDP-43 positive neuronal inclusions, with many neuronal intranuclear inclusions the most characteristic feature [144].

Rare causes of FTLD include disorders associated with neuronal inclusions composed of neuronal intermediate filament proteins, including alpha-internexin [145]. There are also several case reports of atypical MSA presenting with frontal dementia and mimicking PiD except that the inclusion bodies contain α-synuclein rather than tau [146, 147].

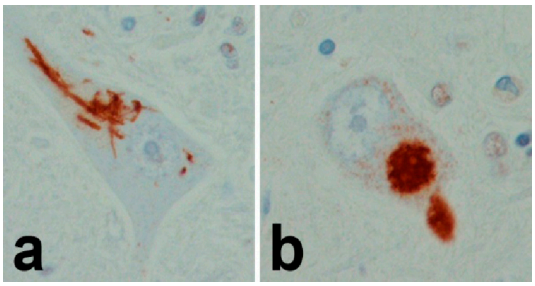

Figure 4. TDP-43 in ALS: Both skein-like (a) and Lewy-like hyaline inclusions (b) are positive for TDP-43.

A recently recognized class of FTLD has neuronal inclusions composed of the protein FUS ("fused in sarcoma") [148], which is also a rare cause of familial ALS [149]. Like TDP-43, FUS is an RNA binding protein that is normally located in the nucleus, with relocation to cytoplasmic inclusions in disease.

Rare cases of FTLD-U have ubiquitinated inclusions for which the protein remains to be determined. One of these is associated with mutations in endosomal ESCRTIII-complex subunit CHMP2B [150]. Sparse TDP-43 ubiquitin positive inclusions are detected in this disorder, but largely confined to the hippocampal dentate fascia [151].

Given the heterogeneity of the pathology of FTLD a proposed nomenclature for this group of disorders is shown in **Table 2** [152]. We have taken the liberty of adding FTLD-AS (for FTLD associated with α-synuclein), since the scheme was meant to be updated as the protein in the ubiquitin immunoreactive neuronal inclusions was discovered, as is the case for the recently added FTLD-FUS [148].

Subclassification of FTLD-TDP

The FTLD-TDP group of disorders has been subclassified based upon characteristic appearance and distribution of the TDP-43 inclusions [153, 154]. We recently expanded the analyses to include multiple subcortical regions of analysis, as was also done by Alafuzoff and co-workers [155]. Like that study, we also found that the classification scheme originally proposed by Mackenzie and co-workers had the best clinicopathologic correlations, and it also was associated with distinctive subcortical pathology [156]. The Mackenzie classification scheme originally took into account only two regions – cortex and hippocampus [154]. We have added amygdala, basal ganglia, thalamus, midbrain and medulla. Mackenzie type 1 (similar to Cairns type 3 [153]) is characterized by superficial cortical spongiosis with pleo-morphic TDP-43 neuronal inclusions and short curvilinear neurites in the same superificial layers (**Figure 5b**). The dentate fascia neurons are affected and have crescent shaped or round

Table 2. Classification of frontotemporal lobar degenerations (adapted from [152])

FTLD-Molecular abnormality	Genetic loci
FTLD-TDP	
Frontotemporal lobar degeneration with TDP-43 inclusions	
Subtype 1 (associated with SD)	None known
Subtype 2 (associated with MND)	Chromosome 9
Subtype 3 (associated with FTDbv and PNFA)	*GRN*
Subtype 4 (associated with Paget's and IBM)	*VCP*
FTLD-TAU	
Frontotemporal lobar degeneration with tauopathy	*MAPT*
Pick's disease (3R tauopathy)	
Corticobasal degeneration (4R tauopathy)	
Progressive supranuclear palsy	
Multisystem tauopathy (4R tauopathy)	
FTLD-IF	
Frontotemporal lobar degeneration with intermediate filament inclusions	None known
FTLD-FUS	
Frontotemporal lobar degeneration with FUS inclusions	*FUS*
FTLD-UPS	
Frontotemporal lobar degeneration with inclusions composed of ubiquitin and other components of ubiquitin-proteasome system (e.g., P62-sequestosome)	*CHMP2b*
FTLD-AS	
Frontotemporal lobar degeneration with inclusions composed of α-synuclein (atypical Pick's disease)	*SNCA?*
FTLD-NI	
Frontotemporal lobar degeneration with no inclusions	None known

FTLD-TDP Subtype 1 = Mackenzie Type 2; FTLD-TDP Subtype 2 = Mackenzie Type 3; FTLD-TDP Subtype 3 = Mackenzie Type 1; FTLD-TDP Subtype 4 = no Mackenzie type assigned.

inclusions (**Figure 5a**). A distinctive histologic feature is the presence of delicate thin neurites in the pyramidal layer of the hippocampus, first reported by Hatanpaa [157] (**Figure 5c**). This form of FTLD-TDP is associated with the most widespread pathology, and there are often inclusions in the amygdala, basal ganglia, thalamus and brainstem. The clinical presentation is FTDbv, PNFA or occasionally CBS. Mutations in *GRN* are associated with this pathology and all such cases have neuronal intranuclear inclusions [158, 159].

Mackenzie type 2 (Cairns type 1) FTLD-TDP is associated with temporal atrophy, especially affecting the dominant hemisphere and associated with SD. The hallmark histo-pathologic lesions are long, thick neurites (**Figure 5f**) with no cortical laminar predilection (**Figure 5e**) often involving the lower cortical layers. There are also Pick-body like inclusions in the dentate fascia (**Figure 5d**), amygdala and basal ganglia. This form of FTLD-TDP has minimal pathology in diencephalon or brainstem.

Mackenzie type 3 (Cairns type 1) is associated with FTLD with motor neuron disease and ALS. There are TDP-43 inclusions in neuronal cell bodies (**Figure 5g**), but few or no neurites. Some of the inclusions have diffuse granular cytoplasmic staining typical of "pre-inclusions' (**Figure 5h**). The dentate fascia is variably affected. This form of FTLD-TDP has a predilection for the frontal cortex and has highly variable involvement in the lower neuroaxis, the exception being the regular involvement of the hypoglossal nucleus (**Figure 5i**), which is affected in cases with motor neuron. Glial inclusions (**Figure 5i, arrow**) are common in this type of FTLD-TDP.

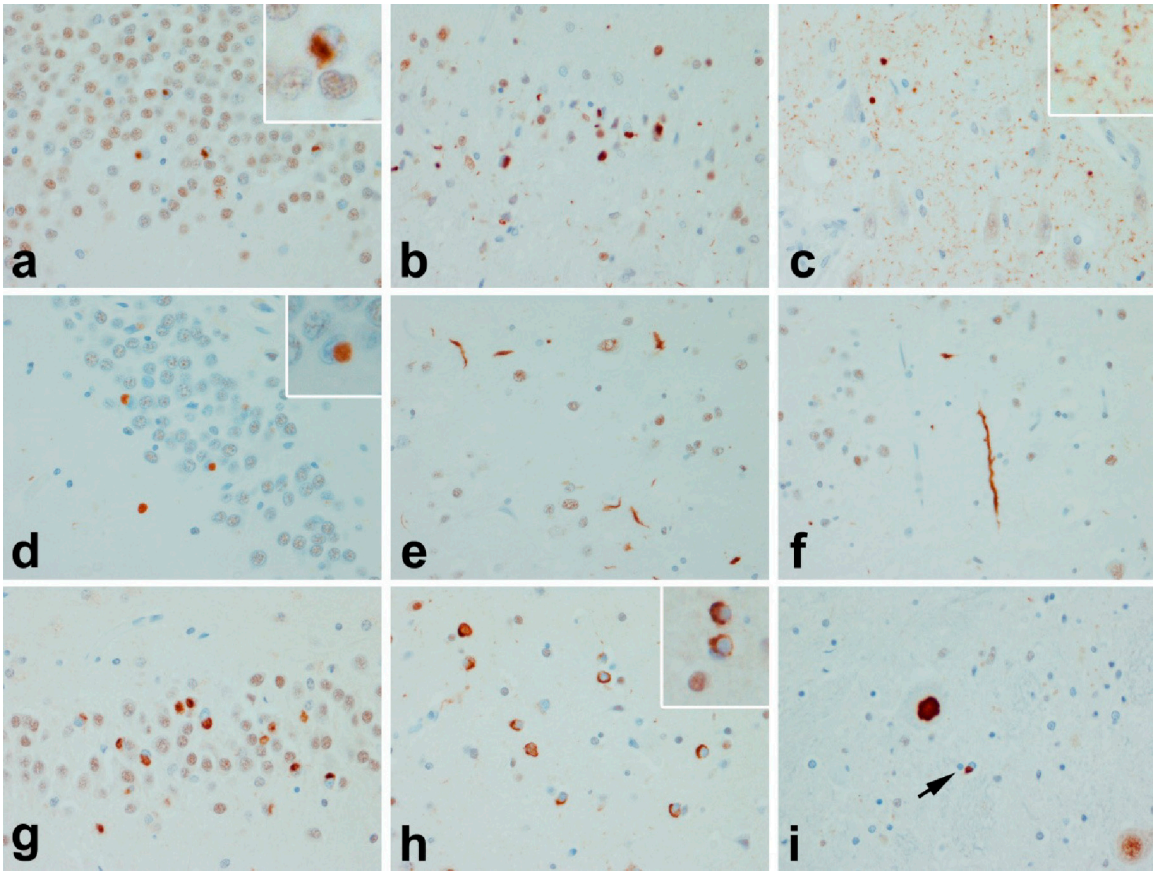

Figure 5. *TDP-43 proteinopathies*: a, b & c FTLD-TDP Type 1; d, e & f FTLD-TDP Type 2; g, h & I FTLD-TDP Type 3. Distinct patterns of TDP-43 pathology define subtypes of TDP-43 proteinopathies. In Type 1 there is widespread pathology in forebrain and hindbrain structures, with neurites and neuronal cytoplasmic inclusions (NCI) in hippocampal dentate fascia (a) and neocortex (b). A characteristic feature of many Type 1 cases is the presence of many small fine neurites in the pyramidal layer of the hippocampus (c). In Type 2 there are round dense NCI in the hippocampal dentate fascia (d) (as well as in the amygdala and basal ganglia), but predominantly long thick neurites in the cortex (e & f). The pathology is minimal in the hindbrain in Type 2. In Type 3 cases the predominant pathology is NCI with a paucity of dystrophic neurites. In addition to the hippocampus (g) and cortex (h), NCI are found in motor neurons of the brainstem and spinal cord (i). Inclusions in Type 3 are similar to those in ALS, with more widespread forebrain involvement in cases with dementia than in those with only motor neuron signs.

TDP-43 pathology in AD

TDP-43 immunoreactive neurons are sometimes detected in the setting of other disorders, particularly AD [131, 160-162], where it may be seen in neurons with neurofibrillary tangles [131]. In many of these cases the TDP-43 pathology is relatively restricted to the limbic lobe and not associated with many dystrophic neurites. It is thus, similar to Mackenzie type 3, but given the co-localization in neurons with tau tangles and the absence of TDP-43 pathology in motor neurons, it is actually a distinct type of TDP-43 proteinopathy. At present, this tangle-associated TDP-43 has not been incorporated into classification schemes for FTLD-TDP and it could be argued that it is a distinct process from FTLD-TDP, analogous to the presence of α-synuclein in limbic lobe neurons, sometimes in neurons with tangles, in AD [81]. The proportion of AD cases with TDP-43 pathology ranges from 20 to 50% depending upon whether tangle-associated TDP-43 is included [131, 160, 163]. Except for our study, where we did not include tangle-associated TDP-43, none of the other reports has made this distinction. It is of interest that TDP-43 associated with Lewy body disorders is also so some extent a function of concurrent AD pathology [132, 160, 161]. Tangle associated TDP-43 appears to be a phenomenon that is relatively unique to 3R+4R tauopathies, such as AD, Guam PDC and in tangle predominant

dementia. In a large series of PSP cases (over 250 cases), we have not seen TDP-43 pathology, except in cases with concurrent AD or hippocampal sclerosis (unpublished observations).

Hippocampal sclerosis (HpScl)

Hippocampal sclerosis (HpScl) is a pathologic finding characterized by neuronal loss in the subiculum and CA1 of the hippocampus. It is a common finding in elderly subjects with dementia, either alone or more often accompanied by other pathologic processes [164-168]. It is even more frequent in FTLD-U, where over 70% of cases have HpScl [169]. Conversely, in studies of HpScl, up to 12% of cases have ubiquitin-immunoreactive inclu-sions similar to FTLD-U [170]. Due to this strong association, when HpScl is detected, it is important to rule out FTLD-U. In our series of HpScl we detected TDP-43 immunoreactivity, most often similar to Mackenzie type 1, in over 70% of cases [131]. In contrast to FTLD-TDP, TDP-43 pathology in HpScl may be limited to limbic lobe structures, particularly the amygdala and entorhinal cortex, rather than being more widespread [131]. This suggests that TDP-43 in the setting of HpScl may be a *forme fruste* of FTLD-TDP. It is important to emphasize that HpScl that occurs in the setting of temporal lobe epilepsy or after cardiac arrest and anoxic brain injury is negative for TDP-43 [131, 171, 172].

When TDP-43 occurs in the setting of other well recognized neurodegenerative disorders, such as AD and HpScl, the significance of this finding is debated. Does it represent concurrent FTLD-TDP or co-deposition of fibrillogenic proteins in a vulnerable set of neurons? Experimental observations by Zhang, and co-workers suggests that TDP-43 becomes more fibrillogenic when it undergoes cleavage and that this cleavage can be promoted by apoptosis [173]. That TDP-43 is vulnerable to proteolytic cleavage comes from global mapping of proteolytic events in apoptosis [174]; TDP-43 is one of the many proteins that is cleaved during apoptosis. In addition, carboxyl terminal fragments of TDP-43 have been shown to be more toxic than full length protein and to have greater propensity to form inclusions [175, 176]. Thus, it could be hypothesized that under certain conditions of cell stress that lead to activation of proteolysis associated with programmed cell death, TDP-43 is cleaved. The cleaved TDP-43 fragments subsequently assemble into filaments aggregates [177]. Thus, TDP-43 inclusions could have more specificity with respect to mechanism of neurodegeneration than to disease type [178].

Concluding remarks

This brief overview of select aspects of non-AD neurodegenerative diseases highlights some common features of these clinically and pathologically diverse disorders. Among these key principles is the importance of abnormal protein conformers, particularly conformers with amyloid-like beta-sheet secondary structure that have a propensity to aggregate either in the extracellular domain or within the cytoplasm of neurons or glia, or both. Another important point is that for most, but not all, of these disorders mutations are found in the gene that encodes the abnormal protein that is found in these aggregates and genetic variants in these genes contribute to increased risk for the disease in sporadic cases. Several examples can be cited: mutations in *MAPT* give rise to FTLD-TAU [179], while genetic variants in *MAPT* predispose to the tauopathies PSP and CBD [180]; mutations in *SNCA* give rise to familial PD [87], while genetic variants in *SNCA* predispose to the α-synucleinopathies PD [181] and MSA [124]; while progranulin does not accumulate in FTLD-TDP, mutations in *GRN* give rise to FTLD-TDP [142] and genetic variants in *GRN* predispose to sporadic FTLD-TDP [182]. Further studies are needed to determine what determine non-genetic risk factors and if there are common mechanisms for selective neuronal vulnerability that is the defining feature of these disorders.

Acknowledgments

The authors thank Virginia Philips, Linda Rousseau and Monica Castanedes-Casey for their expert technical assistance and Wen-Lang Lin for ultrastructural studies. The author acknowledges the assistance of Dr. Tamas Revesz, University College London, for providing tissue samples of FBD and John Steele for providing tissue samples from Guam PDC. This study was supported by NIH grants P50-NS40256, P50-AG25711, P50-AG16574 and P01-AG17216, as well as the State of Florida Alzheimer Disease Initiative, Society for Progressive Supranuclear Palsy and Mayo Foundation for Education and Research.

Please address all correspondences to: Dennis W. Dickson, MD, Neuropathology Laboratory, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL. 32224; Tel: 904-953-7137, Fax: 904-953-7117; E-mail: dickson.dennis@mayo.edu

References

[1] Glenner GG. Amyloid deposits and amyloidosis: the beta-fibrilloses (second of two parts). N Engl J Med 1980; 302: 1333-1343.

[2] Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med 1980; 302: 1283-1292.

[3] Gu Y, Sanjo N, Chen F, Hasegawa H, Petit A, Ruan X, Li W, Shier C, Kawarai T, Schmitt-Ulms G, Westaway D, St George-Hyslop P and Fraser PE. The presenilin proteins are components of multiple membrane-bound complexes that have different biological activities. J Biol Chem 2004; 279: 31329-31336.

[4] Hardy J. Has the amyloid cascade hypothesis for Alzheimer's disease been proved? Curr Alzheimer Res 2006; 3: 71-73.

[5] Braak H and Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997; 18: 351-357.

[6] Dickson DW, Crystal HA, Mattiace LA, Masur DM, Blau AD, Davies P, Yen SH and Aronson MK. Identification of normal and pathological aging in prospectively studied nondemented elderly humans. Neurobiol Aging 1992; 13: 179-189.

[7] Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolko SK, James JA, Snitz BE, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan EM and Klunk WE. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol 2008; 65: 1509-1517.

[8] Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JB, Alexander GE, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, DeKosky ST and Caselli RJ. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc Natl Acad Sci U S A 2009; 106: 6820-6825.

[9] Josephs KA, Tsuboi Y, Cookson N, Watt H and Dickson DW. Apolipoprotein E epsilon 4 is a determinant for Alzheimer-type pathologic features in tauopathies, synucleinopathies, and frontotemporal degeneration. Arch Neurol 2004; 61: 1579-1584.

[10] Strittmatter WJ and Roses AD. Apolipoprotein E and Alzheimer disease. Proc Natl Acad Sci U S A 1995; 92: 4725-4727.

[11] Dickson DW, Crystal H, Mattiace LA, Kress Y, Schwagerl A, Ksiezak-Reding H, Davies P and Yen SH. Diffuse Lewy body disease: light and electron microscopic immunocytochemistry of senile plaques. Acta Neuropathol 1989; 78: 572-584.

[12] Vidal R, Frangione B, Rostagno A, Mead S, Revesz T, Plant G and Ghiso J. A stop-codon mutation in the BRI gene associated with familial British dementia. Nature 1999; 399: 776-781.

[13] Holton JL, Ghiso J, Lashley T, Rostagno A, Guerin CJ, Gibb G, Houlden H, Ayling H, Martinian L, Anderton BH, Wood NW, Vidal R, Plant G, Frangione B and Revesz T. Regional distribution of amyloid-Bri deposition and its association with neurofibrillary degeneration in familial British dementia. Am J Pathol 2001; 158: 515-526.

[14] Ironside JW, Head MW, Bell JE, McCardle L and Will RG. Laboratory diagnosis of variant Creutzfeldt-Jakob disease. Histopathology 2000; 37: 1-9.

[15] Capellari S, Vital C, Parchi P, Petersen RB, Ferrer X, Jarnier D, Pegoraro E, Gambetti P and Julien J. Familial prion disease with a novel 144-bp insertion in the prion protein gene in a Basque family. Neurology 1997; 49: 133-141.

[16] Bugiani O, Giaccone G, Piccardo P, Morbin M, Tagliavini F and Ghetti B. Neuropathology of Gerstmann-Straussler-Scheinker disease. Microsc Res Tech 2000; 50: 10-15.

[17] Gajdusek DC and Zigas V. Kuru; clinical, pathological and epidemiological study of an acute progressive degenerative disease of the central nervous system among natives of the Eastern Highlands of New Guinea. Am J Med 1959; 26: 442-469.

[18] Parchi P, Giese A, Capellari S, Brown P, Schulz-Schaeffer W, Windl O, Zerr I, Budka H, Kopp N, Piccardo P, Poser S, Rojiani A, Streichemberger N, Julien J, Vital C, Ghetti B, Gambetti P and Kretzschmar H. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999; 46: 224-233.

[19] Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, McCardle L, Chree A, Hope J, Birkett C, Cousens S, Fraser H and Bostock CJ. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 1997; 389: 498-501.

[20] Collinge J, Sidle KC, Meads J, Ironside J and Hill AF. Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD. Nature 1996; 383: 685-690.

[21] Ghetti B, Dlouhy SR, Giaccone G, Bugiani O, Frangione B, Farlow MR and Tagliavini F.

Gerstmann-Straussler-Scheinker disease and the Indiana kindred. Brain Pathol 1995; 5: 61-75.

[22] Giaccone G, Tagliavini F, Verga L, Frangione B, Farlow MR, Bugiani O and Ghetti B. Neurofibrillary tangles of the Indiana kindred of Gerstmann-Straussler-Scheinker disease share antigenic determinants with those of Alzheimer disease. Brain Res 1990; 530: 325-329.

[23] Azzarelli B, Muller J, Ghetti B, Dyken M and Conneally PM. Cerebellar plaques in familial Alzheimer's disease (Gerstmann-Straussler-Scheinker variant?). Acta Neuropathol 1985; 65: 235-246.

[24] Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS and Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J Biol Chem 1986; 261: 6084-6089.

[25] Binder LI, Frankfurter A and Rebhun LI. The distribution of tau in the mammalian central nervous system. J Cell Biol 1985; 101: 1371-1378.

[26] Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N, Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T and Heutink P. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393: 702-705.

[27] Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P and Hutton M. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet 2000; 25: 402-405.

[28] Andreadis A, Brown WM and Kosik KS. Structure and novel exons of the human tau gene. Biochemistry 1992; 31: 10626-10633.

[29] Goedert M, Spillantini MG, Potier MC, Ulrich J and Crowther RA. Cloning and sequencing of the cDNA encoding an isoform of microtubule-associated protein tau containing four tandem repeats: differential expression of tau protein mRNAs in human brain. Embo J 1989; 8: 393-399.

[30] Togo T, Sahara N, Yen SH, Cookson N, Ishizawa T, Hutton M, de Silva R, Lees A and Dickson DW. Argyrophilic grain disease is a sporadic 4-repeat tauopathy. J Neuropathol Exp Neurol 2002; 61: 547-556.

[31] Tolnay M and Clavaguera F. Argyrophilic grain disease: a late-onset dementia with distinctive features among tauopathies. Neuropathology 2004; 24: 269-283.

[32] Jicha GA, Petersen RC, Knopman DS, Boeve BF, Smith GE, Geda YE, Johnson KA, Cha R, Delucia MW, Braak H, Dickson DW and Parisi JE. Argyrophilic grain disease in demented subjects presenting initially with amnestic mild cognitive impairment. J Neuropathol Exp Neurol 2006; 65: 602-609.

[33] Togo T, Cookson N and Dickson DW. Argyrophilic grain disease: neuropathology, frequency in a dementia brain bank and lack of relationship with apolipoprotein E. Brain Pathol 2002; 12: 45-52.

[34] Braak H and Braak E. Argyrophilic grain disease: frequency of occurrence in different age categories and neuropathological diagnostic criteria. J Neural Transm 1998; 105: 801-819.

[35] Tolnay M, Mistl C, Ipsen S and Probst A. Argyrophilic grains of Braak: occurrence in dendrites of neurons containing hyperphosphorylated tau protein. Neuropathol Appl Neurobiol 1998; 24: 53-59.

[36] Braak H and Braak E. Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. Neurosci Lett 1987; 76: 124-127.

[37] Botez G, Probst A, Ipsen S and Tolnay M. Astrocytes expressing hyperphosphorylated tau protein without glial fibrillary tangles in argyrophilic grain disease. Acta Neuropathol 1999; 98: 251-256.

[38] Tolnay M and Probst A. Ballooned neurons expressing alphaB-crystallin as a constant feature of the amygdala in argyrophilic grain disease. Neurosci Lett 1998; 246: 165-168.

[39] Fujino Y, Wang DS, Thomas N, Espinoza M, Davies P and Dickson DW. Increased frequency of argyrophilic grain disease in Alzheimer disease with 4R tau-specific immunohisto-chemistry. J Neuropathol Exp Neurol 2005; 64: 209-214.

[40] Schneider JA, Arvanitakis Z, Bang W and Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007; 69: 2197-2204.

[41] Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H and

Kokmen E. Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol 2006; 63: 665-672.

[42] Maurage CA, Sergeant N, Schraen-Maschke S, Lebert F, Ruchoux MM, Sablonniere B, Pasquier F and Delacourte A. Diffuse form of argyrophilic grain disease: a new variant of four-repeat tauopathy different from limbic argyrophilic grain disease. Acta Neuropathol 2003; 106: 575-583.

[43] Litvan I, Grimes DA and Lang AE. Phenotypes and prognosis: clinicopathologic studies of corticobasal degeneration. Adv Neurol 2000; 82: 183-196.

[44] Kertesz A, Martinez-Lage P, Davidson W and Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology 2000; 55: 1368-1375.

[45] Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, Jellinger K, Lantos PL, Lippa CF, Mirra SS, Tabaton M, Vonsattel JP, Wakabayashi K and Litvan I. Office of Rare Diseases neuropathologic criteria for cortico-basal degeneration. J Neuropathol Exp Neurol 2002; 61: 935-946.

[46] Feany MB and Dickson DW. Widespread cytoskeletal pathology characterizes corticobasal degeneration. Am J Pathol 1995; 146: 1388-1396.

[47] Komori T, Arai N, Oda M, Nakayama H, Mori H, Yagishita S, Takahashi T, Amano N, Murayama S, Murakami S, Shibata N, Kobayashi M, Sasaki S and Iwata M. Astrocytic plaques and tufts of abnormal fibers do not coexist in corticobasal degeneration and progressive supranuclear palsy. Acta Neuropathol 1998; 96: 401-408.

[48] Rebeiz JJ, Kolodny EH and Richardson EP, Jr. Corticodentatonigral degeneration with neuronal achromasia: a progressive disorder of late adult life. Trans Am Neurol Assoc 1967; 92: 23-26.

[49] Steele JC, Richardson JC and Olszewski J. Progressive Supranuclear Palsy. a Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum with Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia. Arch Neurol 1964; 10: 333-359.

[50] Bigio EH, Brown DF and White CL, 3rd. Progressive supranuclear palsy with dementia: cortical pathology. J Neuropathol Exp Neurol 1999; 58: 359-364.

[51] Josephs KA, Boeve BF, Duffy JR, Smith GE, Knopman DS, Parisi JE, Petersen RC and Dickson DW. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. Neurocase 2005; 11: 283-296.

[52] Josephs KA, Katsuse O, Beccano-Kelly DA, Lin WL, Uitti RJ, Fujino Y, Boeve BF, Hutton ML, Baker MC and Dickson DW. Atypical progressive supranuclear palsy with corticospinal tract degeneration. J Neuropathol Exp Neurol 2006; 65: 396-405.

[53] Ahmed Z, Josephs KA, Gonzalez J, DelleDonne A and Dickson DW. Clinical and neuropathologic features of progressive supranuclear palsy with severe pallido-nigro-luysial degeneration and axonal dystrophy. Brain 2008; 131: 460-472.

[54] Williams DR, Holton JL, Strand K, Revesz T and Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord 2007; 22: 2235-2241.

[55] Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, Holton JL, Revesz T and Lees AJ. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 2005; 128: 1247-1258.

[56] Tsuboi Y, Josephs KA, Boeve BF, Litvan I, Caselli RJ, Caviness JN, Uitti RJ, Bott AD and Dickson DW. Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. Mov Disord 2005; 20: 982-988.

[57] Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, McKee A, Tabaton M and Litvan I. Preliminary NINDS neuro-pathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994; 44: 2015-2019.

[58] Tsuboi Y, Slowinski J, Josephs KA, Honer WG, Wszolek ZK and Dickson DW. Atrophy of superior cerebellar peduncle in progressive supranuclear palsy. Neurology 2003; 60: 1766-1769.

[59] Nilsson C, Markenroth Bloch K, Brockstedt S, Latt J, Widner H and Larsson EM. Tracking the neurodegeneration of parkinsonian disorders – a pilot study. Neuroradiology 2007; 49: 111-119.

[60] Yamada T, McGeer PL and McGeer EG. Appearance of paired nucleated, Tau-positive glia in patients with progressive supranuclear palsy brain tissue. Neurosci Lett 1992; 135: 99-102.

[61] Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Shepherd E, Sevush S, Graff-Radford N, Newland D, Todd M, Miller B, Gold M, Heilman K, Doty L, Goodman I, Robinson B, Pearl G, Dickson D and Duara R. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and

hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord 2002; 16: 203-212.

[62] Bronner IF, ter Meulen BC, Azmani A, Severijnen LA, Willemsen R, Kamphorst W, Ravid R, Heutink P and van Swieten JC. Hereditary Pick's disease with the G272V tau mutation shows predominant three-repeat tau pathology. Brain 2005; 128: 2645-2653.

[63] Hogg M, Grujic ZM, Baker M, Demirci S, Guillozet AL, Sweet AP, Herzog LL, Weintraub S, Mesulam MM, LaPointe NE, Gamblin TC, Berry RW, Binder LI, de Silva R, Lees A, Espinoza M, Davies P, Grover A, Sahara N, Ishizawa T, Dickson D, Yen SH, Hutton M and Bigio EH. The L266V tau mutation is associated with frontotemporal dementia and Pick-like 3R and 4R tauopathy. Acta Neuropathol 2003; 106: 323-336.

[64] Buee L and Delacourte A. Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick's disease. Brain Pathol 1999; 9: 681-693.

[65] de Silva R, Lashley T, Strand C, Shiarli AM, Shi J, Tian J, Bailey KL, Davies P, Bigio EH, Arima K, Iseki E, Murayama S, Kretzschmar H, Neumann M, Lippa C, Halliday G, MacKenzie J, Ravid R, Dickson D, Wszolek Z, Iwatsubo T, Pickering-Brown SM, Holton J, Lees A, Revesz T and Mann DM. An immunohistochemical study of cases of sporadic and inherited frontotemporal lobar degeneration using 3R- and 4R-specific tau monoclonal antibodies. Acta Neuropathol 2006; 111: 329-340.

[66] Zhukareva V, Mann D, Pickering-Brown S, Uryu K, Shuck T, Shah K, Grossman M, Miller BL, Hulette CM, Feinstein SC, Trojanowski JQ and Lee VM. Sporadic Pick's disease: a tauopathy characterized by a spectrum of pathological tau isoforms in gray and white matter. Ann Neurol 2002; 51: 730-739.

[67] Yoshimura N. Topography of Pick body distribution in Pick's disease: a contribution to understanding the relationship between Pick's and Alzheimer's diseases. Clin Neuropathol 1989; 8: 1-6.

[68] Hansen LA, Deteresa R, Tobias H, Alford M and Terry RD. Neocortical morphometry and cholinergic neurochemistry in Pick's disease. Am J Pathol 1988; 131: 507-518.

[69] Iseki E, Yamamoto R, Murayama N, Minegishi M, Togo T, Katsuse O, Kosaka K, Akiyama H, Tsuchiya K, de Silva R, Andrew L and Arai H. Immunohistochemical investigation of neurofibrillary tangles and their tau isoforms in brains of limbic neurofibrillary tangle dementia. Neurosci Lett 2006; 405: 29-33.

[70] Ikeda K, Akiyama H, Arai T, Oda T, Kato M, Iseki E, Kosaka K, Wakabayashi K and Takahashi H. Clinical aspects of 'senile dementia of the tangle type'-- a subset of dementia in the senium separable from late-onset Alzheimer's disease. Dement Geriatr Cogn Disord 1999; 10: 6-11.

[71] Ikeda K, Akiyama H, Arai T, Sahara N, Mori H, Usami M, Sakata M, Mizutani T, Wakabayashi K and Takahashi H. A subset of senile dementia with high incidence of the apolipoprotein E epsilon2 allele. Ann Neurol 1997; 41: 693-695.

[72] Jellinger KA and Attems J. Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. Acta Neuropathol 2007; 113: 107-117.

[73] Jellinger KA and Bancher C. Senile dementia with tangles (tangle predominant form of senile dementia). Brain Pathol 1998; 8: 367-376.

[74] Braak H and Braak E. Neurofibrillary changes confined to the entorhinal region and an abundance of cortical amyloid in cases of presenile and senile dementia. Acta Neuropathol 1990; 80: 479-486.

[75] Hirano A, Kurland LT, Krooth RS and Lessell S. Parkinsonism-dementia complex, an endemic disease on the island of Guam. I. Clinical features. Brain 1961; 84: 642-661.

[76] Hirano A, Malamud N and Kurland LT. Parkinsonism-dementia complex, an endemic disease on the island of Guam. II. Pathological features. Brain 1961; 84: 662-679.

[77] Kuzuhara S and Kokubo Y. Atypical parkinsonism of Japan: amyotrophic lateral sclerosis-parkinsonism-dementia complex of the Kii peninsula of Japan (Muro disease): an update. Mov Disord 2005; 20 Suppl 12: S108-113.

[78] Morris HR, Steele JC, Crook R, Wavrant-De Vrieze F, Onstead-Cardinale L, Gwinn-Hardy K, Wood NW, Farrer M, Lees AJ, McGeer PL, Siddique T, Hardy J and Perez-Tur J. Genome-wide analysis of the parkinsonism-dementia complex of Guam. Arch Neurol 2004; 61: 1889-1897.

[79] Buee-Scherrer V, Buee L, Hof PR, Leveugle B, Gilles C, Loerzel AJ, Perl DP and Delacourte A. Neurofibrillary degeneration in amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam. Immunochemical characterization of tau proteins. Am J Pathol 1995; 146: 924-932.

[80] Forman MS, Schmidt ML, Kasturi S, Perl DP, Lee VM and Trojanowski JQ. Tau and alpha-synuclein pathology in amygdala of Parkinsonism-dementia complex patients of Guam. Am J Pathol 2002; 160: 1725-1731.

[81] Uchikado H, Lin WL, DeLucia MW and Dickson DW. Alzheimer disease with amygdala Lewy bodies: a distinct form of alpha-synucleinopathy. J Neuropathol Exp Neurol 2006; 65: 685-697.
[82] Hasegawa M, Arai T, Akiyama H, Nonaka T, Mori H, Hashimoto T, Yamazaki M and Oyanagi K. TDP-43 is deposited in the Guam parkinsonism-dementia complex brains. Brain 2007; 130: 1386-1394.
[83] Geser F, Winton MJ, Kwong LK, Xu Y, Xie SX, Igaz LM, Garruto RM, Perl DP, Galasko D, Lee VM and Trojanowski JQ. Pathological TDP-43 in parkinsonism-dementia complex and amyo-trophic lateral sclerosis of Guam. Acta Neuropathol 2008; 115: 133-145.
[84] Clayton DF and George JM. The synucleins: a family of proteins involved in synaptic function, plasticity, neurodegeneration and disease. Trends Neurosci 1998; 21: 249-254.
[85] Iwai A, Masliah E, Sundsmo MP, DeTeresa R, Mallory M, Salmon DP and Saitoh T. The synaptic protein NACP is abnormally expressed during the progression of Alzheimer's disease. Brain Res 1996; 720: 230-234.
[86] Masliah E, Iwai A, Mallory M, Ueda K and Saitoh T. Altered presynaptic protein NACP is associated with plaque formation and neurodegeneration in Alzheimer's disease. Am J Pathol 1996; 148: 201-210.
[87] Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI and Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 1997; 276: 2045-2047.
[88] Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R and Goedert M. Alpha-synuclein in Lewy bodies. Nature 1997; 388: 839-840.
[89] Gibb WR. Idiopathic Parkinson's disease and the Lewy body disorders. Neuropathol Appl Neurobiol 1986; 12: 223-234.
[90] Popescu A, Lippa CF, Lee VM and Trojanowski JQ. Lewy bodies in the amygdala: increase of alpha-synuclein aggregates in neurodegenera-tive diseases with tau-based inclusions. Arch Neurol 2004; 61: 1915-1919.
[91] Uchikado H and Dickson DW. Presence of Lewy bodies in progressive supranuclear palsy represents an independent disease process. J Neuropathol Exp Neurol 2005; 64: 450-450.
[92] Lippa CF, Schmidt ML, Lee VM and Trojanowski JQ. Antibodies to alpha-synuclein detect Lewy bodies in many Down's syndrome brains with Alzheimer's disease. Ann Neurol 1999; 45: 353-357.
[93] Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. Brain Pathol 2000; 10: 378-384.
[94] Newell KL, Boyer P, Gomez-Tortosa E, Hobbs W, Hedley-Whyte ET, Vonsattel JP and Hyman BT. Alpha-synuclein immunoreactivity is present in axonal swellings in neuroaxonal dystrophy and acute traumatic brain injury. J Neuropathol Exp Neurol 1999; 58: 1263-1268.
[95] Arawaka S, Saito Y, Murayama S and Mori H. Lewy body in neurodegeneration with brain iron accumulation type 1 is immunoreactive for alpha-synuclein. Neurology 1998; 51: 887-889.
[96] Greffard S, Verny M, Bonnet AM, Beinis JY, Gallinari C, Meaume S, Piette F, Hauw JJ and Duyckaerts C. Motor score of the Unified Parkinson Disease Rating Scale as a good predictor of Lewy body-associated neuronal loss in the substantia nigra. Arch Neurol 2006; 63: 584-588.
[97] Boeve BF, Silber MH, Ferman TJ, Lucas JA and Parisi JE. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001; 16: 622-630.
[98] Miyamoto T, Miyamoto M, Inoue Y, Usui Y, Suzuki K and Hirata K. Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. Neurology 2006; 67: 2236-2238.
[99] Stiasny-Kolster K, Doerr Y, Moller JC, Hoffken H, Behr TM, Oertel WH and Mayer G. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. Brain 2005; 128: 126-137.
[100] Aarsland D, Perry R, Brown A, Larsen JP and Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005; 58: 773-776.
[101] Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN and Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24: 197-211.
[102] Braak H, Bohl JR, Muller CM, Rub U, de Vos RA and Del Tredici K. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006; 21: 2042-2051.
[103] Braak H and Del Tredici K. Neuroanatomy and pathology of sporadic Parkinson's disease. Adv Anat Embryol Cell Biol 2009; 201: 1-119.
[104] Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, Spencer B, Masliah E and

Lee SJ. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proc Natl Acad Sci U S A 2009; 106: 13010-13015.

[105] Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Bjorklund A, Widner H, Revesz T, Lindvall O and Brundin P. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 2008; 14: 501-503.

[106] Kordower JH, Chu Y, Hauser RA, Freeman TB and Olanow CW. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 2008; 14: 504-506.

[107] Frost B and Diamond MI. The expanding realm of prion phenomena in neurodegenerative disease. Prion 2009; 3: 74-77.

[108] McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, Dickson D, Dubois B, Duda JE, Feldman H, Gauthier S, Halliday G, Lawlor B, Lippa C, Lopez OL, Carlos Machado J, O'Brien J, Playfer J and Reid W. Dementia with Lewy bodies. Lancet Neurol 2004; 3: 19-28.

[109] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ and Yamada M. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65: 1863-1872.

[110] Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, Brooks DJ, Dickson DW, Dubois B, Emre M, Fahn S, Farmer JM, Galasko D, Galvin JE, Goetz CG, Growdon JH, Gwinn-Hardy KA, Hardy J, Heutink P, Iwatsubo T, Kosaka K, Lee VM, Leverenz JB, Masliah E, McKeith IG, Nussbaum RL, Olanow CW, Ravina BM, Singleton AB, Tanner CM, Trojanowski JQ and Wszolek ZK. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 2007; 68: 812-819.

[111] Fujishiro H, Ferman TJ, Boeve BF, Smith GE, Graff-Radford NR, Uitti RJ, Wszolek ZK, Knopman DS, Petersen RC, Parisi JE and Dickson DW. Validation of the neuropathologic criteria of the third consortium for dementia with Lewy bodies for prospectively diagnosed cases. J Neuropathol Exp Neurol 2008; 67: 649-656.

[112] Saito Y, Kawashima A, Ruberu NN, Fujiwara H, Koyama S, Sawabe M, Arai T, Nagura H, Yamanouchi H, Hasegawa M, Iwatsubo T and Murayama S. Accumulation of phosphorylated alpha-synuclein in aging human brain. J Neuropathol Exp Neurol 2003; 62: 644-654.

[113] Dickson DW, Ruan D, Crystal H, Mark MH, Davies P, Kress Y and Yen SH. Hippocampal degeneration differentiates diffuse Lewy body disease (DLBD) from Alzheimer's disease: light and electron microscopic immunocytochemistry of CA2-3 neurites specific to DLBD. Neurology 1991; 41: 1402-1409.

[114] Dickson DW, Schmidt ML, Lee VM, Zhao ML, Yen SH and Trojanowski JQ. Immunoreactivity profile of hippocampal CA2/3 neurites in diffuse Lewy body disease. Acta Neuropathol 1994; 87: 269-276.

[115] Bertrand E, Lechowicz W, Szpak GM, Lewandowska E, Dymecki J and Wierzba-Bobrowicz T. Limbic neuropathology in idio-pathic Parkinson's disease with concomi-tant dementia. Folia Neuropathol 2004; 42: 141-150.

[116] Apaydin H, Ahlskog JE, Parisi JE, Boeve BF and Dickson DW. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. Arch Neurol 2002; 59: 102-112.

[117] Churchyard A and Lees AJ. The relationship between dementia and direct involvement of the hippocampus and amygdala in Parkinson's disease. Neurology 1997; 49: 1570-1576.

[118] Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, Clark CM, Glosser G, Stern MB, Gollomp SM and Arnold SE. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 2000; 54: 1916-1921.

[119] Colosimo C, Hughes AJ, Kilford L and Lees AJ. Lewy body cortical involvement may not always predict dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 2003; 74: 852-856.

[120] Parkkinen L, Kauppinen T, Pirttila T, Autere JM and Alafuzoff I. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann Neurol 2005; 57: 82-91.

[121] Zaccai J, Brayne C, McKeith I, Matthews F and Ince PG. Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. Neurology 2008; 70: 1042-1048.

[122] Gwinn-Hardy K, Mehta ND, Farrer M, Maraganore D, Muenter M, Yen SH, Hardy J and Dickson DW. Distinctive neuropathology revealed by alpha-synuclein antibodies in hereditary parkinsonism and dementia linked to chromosome 4p. Acta Neuropathol (Berl) 2000; 99: 663-672.

[123] Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, Kaufmann H, Klockgether T, Lang AE, Lantos PL, Litvan I, Mathias CJ, Oliver E, Robertson D, Schatz I and Wenning GK. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999; 163: 94-98.

[124] Scholz SW, Houlden H, Schulte C, Sharma M, Li A, Berg D, Melchers A, Paudel R, Gibbs JR, Simon-Sanchez J, Paisan-Ruiz C, Bras J, Ding J, Chen H, Traynor BJ, Arepalli S, Zonozi RR, Revesz T, Holton J, Wood N, Lees A, Oertel W, Wullner U, Goldwurm S, Pellecchia MT, Illig T, Riess O, Fernandez HH, Rodriguez RL, Okun MS, Poewe W, Wenning GK, Hardy JA, Singleton AB and Gasser T. SNCA variants are associated with increased risk for multiple system atrophy. Ann Neurol 2009; 65: 610-614.

[125] Lantos PL. The definition of multiple system atrophy: a review of recent developments. J Neuropathol Exp Neurol 1998; 57: 1099-1111.

[126] Lin WL, DeLucia MW and Dickson DW. Alpha-synuclein immunoreactivity in neuronal nuclear inclusions and neurites in multiple system atrophy. Neurosci Lett 2004; 354: 99-102.

[127] Wang IF, Wu LS and Shen CK. TDP-43: an emerging new player in neurodegenerative diseases. Trends Mol Med 2008; 14: 479-485.

[128] Wang IF, Wu LS, Chang HY and Shen CK. TDP-43, the signature protein of FTLD-U, is a neuronal activity-responsive factor. J Neurochem 2008; 105: 797-806.

[129] Yamasaki S and Anderson P. Reprogramming mRNA translation during stress. Curr Opin Cell Biol 2008; 20: 222-226.

[130] Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ and Lee VM. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006; 314: 130-133.

[131] Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, Graff-Radford NR, Hutton ML and Dickson DW. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol 2007; 61: 435-445.

[132] Nakashima-Yasuda H, Uryu K, Robinson J, Xie SX, Hurtig H, Duda JE, Arnold SE, Siderowf A, Grossman M, Leverenz JB, Woltjer R, Lopez OL, Hamilton R, Tsuang DW, Galasko D, Masliah E, Kaye J, Clark CM, Montine TJ, Lee VM and Trojanowski JQ. Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. Acta Neuropathol 2007; 114: 221-229.

[133] Kato S, Shaw P, Wood-Allum C, Leigh PN and Shaw C. Amyotrophic lateral sclerosis. In: Dickson DW, editors. Neurodegeneration: The molecular pathology of dementia and movement disorders. Basel: ISN Neuropath Press; 2003. p. 350-368.

[134] Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, O'Regan JP, Deng HX and et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 1993; 362: 59-62.

[135] Greenway MJ, Andersen PM, Russ C, Ennis S, Cashman S, Donaghy C, Patterson V, Swingler R, Kieran D, Prehn J, Morrison KE, Green A, Acharya KR, Brown RH, Jr. and Hardiman O. ANG mutations segregate with familial and 'sporadic' amyotrophic lateral sclerosis. Nat Genet 2006; 38: 411-413.

[136] Sreedharan J, Blair IP, Tripathi VB, Hu X, Vance C, Rogelj B, Ackerley S, Durnall JC, Williams KL, Buratti E, Baralle F, de Belleroche J, Mitchell JD, Leigh PN, Al-Chalabi A, Miller CC, Nicholson G and Shaw CE. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. Science 2008; 319: 1668-1672.

[137] Kovacs GG, Murrell JR, Horvath S, Haraszti L, Majtenyi K, Molnar MJ, Budka H, Ghetti B and Spina S. TARDBP variation associated with frontotemporal dementia, supranuclear gaze palsy, and chorea. Mov Disord 2009;

[138] Okamoto K, Hirai S, Amari M, Watanabe M and Sakurai A. Bunina bodies in amyotrophic lateral sclerosis immunostained with rabbit anti-cystatin C serum. Neurosci Lett 1993; 162: 125-128.

[139] Mackenzie IR, Bigio EH, Ince PG, Geser F, Neumann M, Cairns NJ, Kwong LK, Forman MS, Ravits J, Stewart H, Eisen A, McClusky L, Kretzschmar HA, Monoranu CM, Highley JR, Kirby J, Siddique T, Shaw PJ, Lee VM and Trojanowski JQ. Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. Ann Neurol 2007; 61: 427-434.

[140] McKhann GM, Albert MS, Grossman M, Miller B, Dickson D and Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001; 58: 1803-1809.

[141] Wider C and Wszolek ZK. Etiology and pathophysiology of frontotemporal dementia, Parkinson disease and Alzheimer disease: lessons from genetic studies. Neurodegener Dis 2008; 5: 122-125.

[142] Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S,

Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H and Hutton M. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442: 916-919.

[143] Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, Pestronk A, Whyte MP and Kimonis VE. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat Genet 2004; 36: 377-381.

[144] Forman MS, Mackenzie IR, Cairns NJ, Swanson E, Boyer PJ, Drachman DA, Jhaveri BS, Karlawish JH, Pestronk A, Smith TW, Tu PH, Watts GD, Markesbery WR, Smith CD and Kimonis VE. Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. J Neuropathol Exp Neurol 2006; 65: 571-581.

[145] Cairns NJ, Grossman M, Arnold SE, Burn DJ, Jaros E, Perry RH, Duyckaerts C, Stankoff B, Pillon B, Skullerud K, Cruz-Sanchez FF, Bigio EH, Mackenzie IR, Gearing M, Juncos JL, Glass JD, Yokoo H, Nakazato Y, Mosaheb S, Thorpe JR, Uryu K, Lee VM and Trojanowski JQ. Clinical and neuropathologic variation in neuronal intermediate filament inclusion disease. Neurology 2004; 63: 1376-1384.

[146] Horoupian DS and Dickson DW. Striatonigral degeneration, olivopontocerebellar atrophy and "atypical" Pick disease. Acta Neuropathol (Berl) 1991; 81: 287-295.

[147] Konagaya M, Sakai M, Matsuoka Y, Konagaya Y and Hashizume Y. Multiple system atrophy with remarkable frontal lobe atrophy. Acta Neuropathol 1999; 97: 423-428.

[148] Neumann M, Rademakers R, Roeber S, Baker M, Kretzschmar HA and Mackenzie IR. Frontotemporal lobar degeneration with FUS pathology. Brain 2009;

[149] Kwiatkowski TJ, Jr., Bosco DA, Leclerc AL, Tamrazian E, Vanderburg CR, Russ C, Davis A, Gilchrist J, Kasarskis EJ, Munsat T, Valdmanis P, Rouleau GA, Hosler BA, Cortelli P, de Jong PJ, Yoshinaga Y, Haines JL, Pericak-Vance MA, Yan J, Ticozzi N, Siddique T, McKenna-Yasek D, Sapp PC, Horvitz HR, Landers JE and Brown RH, Jr. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. Science 2009; 323: 1205-1208.

[150] Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, Nielsen JE, Hodges JR, Spillantini MG, Thusgaard T, Brandner S, Brun A, Rossor MN, Gade A, Johannsen P, Sorensen SA, Gydesen S, Fisher EM and Collinge J. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. Nat Genet 2005; 37: 806-808.

[151] Holm IE, Englund E, Mackenzie IR, Johannsen P and Isaacs AM. A reassessment of the neuropathology of frontotemporal dementia linked to chromosome 3. J Neuropathol Exp Neurol 2007; 66: 884-891.

[152] Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJ, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ and Mann DM. Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. Acta Neuropathol 2009; 117: 15-18.

[153] Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL, 3rd, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ and Mann DM. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 2007; 114: 5-22.

[154] Mackenzie IR, Baborie A, Pickering-Brown S, Du Plessis D, Jaros E, Perry RH, Neary D, Snowden JS and Mann DM. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. Acta Neuropathol 2006; 112: 539-549.

[155] Pikkarainen M, Hartikainen P and Alafuzoff I. Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclu-sions visualized with ubiquitin-binding protein p62 immunohistochemistry. J Neuropathol Exp Neurol 2008; 67: 280-298.

[156] Josephs KA, Stroh A, Dugger B and Dickson DW. Evaluation of subcortical pathology and clinical correlations in FTLD-U subtypes. Acta Neuropathol 2009; 118: 349-358.

[157] Hatanpaa KJ, Bigio EH, Cairns NJ, Womack KB, Weintraub S, Morris JC, Foong C, Xiao G, Hladik C, Mantanona TY and White CL, 3rd. TAR DNA-binding protein 43 immunohistochemistry reveals extensive neuritic pathology in FTLD-U: a midwest-southwest consortium for FTLD study. J Neuropathol Exp Neurol 2008; 67: 271-279.

[158] Mackenzie IR, Baker M, Pickering-Brown S, Hsiung GY, Lindholm C, Dwosh E, Gass J, Cannon A, Rademakers R, Hutton M and Feldman HH. The neuropathology of frontotemporal lobar degeneration caused by

mutations in the progranulin gene. Brain 2006; 129: 3081-3090.
[159] Josephs KA, Ahmed Z, Katsuse O, Parisi JF, Boeve BF, Knopman DS, Petersen RC, Davies P, Duara R, Graff-Radford NR, Uitti RJ, Rademakers R, Adamson J, Baker M, Hutton ML and Dickson DW. Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (PGRN) mutations. J Neuropathol Exp Neurol 2007; 66: 142-151.
[160] Arai T, Mackenzie IR, Hasegawa M, Nonoka T, Niizato K, Tsuchiya K, Iritani S, Onaya M and Akiyama H. Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. Acta Neuropathol 2009; 117: 125-136.
[161] Higashi S, Iseki E, Yamamoto R, Minegishi M, Hino H, Fujisawa K, Togo T, Katsuse O, Uchikado H, Furukawa Y, Kosaka K and Arai H. Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. Brain Res 2007; 1184C: 284-294.
[162] Josephs KA, Whitwell JL, Knopman DS, Hu WT, Stroh DA, Baker M, Rademakers R, Boeve BF, Parisi JE, Smith GE, Ivnik RJ, Petersen RC, Jack CR, Jr. and Dickson DW. Abnormal TDP-43 immunoreactivity in AD modifies clinic-pathologic and radiologic phenotype. Neurology 2008; 70: 1850-1857.
[163] Hu WT, Josephs KA, Knopman DS, Boeve BF, Dickson DW, Petersen RC and Parisi JE. Temporal lobar predominance of TDP-43 neuronal cytoplasmic inclusions in Alzheimer disease. Acta Neuropathol 2008; 116: 215-220.
[164] Ala TA, Beh GO and Frey WH, 2nd. Pure hippocampal sclerosis: a rare cause of dementia mimicking Alzheimer's disease. Neurology 2000; 54: 843-848.
[165] Amador-Ortiz C and Dickson DW. Neuropathology of hippocampal sclerosis. Handb Clin Neurol 2008; 89: 569-572.
[166] Attems J and Jellinger KA. Hippocampal sclerosis in Alzheimer disease and other dementias. Neurology 2006; 66: 775.
[167] Corey-Bloom J, Sabbagh MN, Bondi MW, Hansen L, Alford MF, Masliah E and Thal LJ. Hippocampal sclerosis contributes to dementia in the elderly. Neurology 1997; 48: 154-160.
[168] Dickson DW, Davies P, Bevona C, Van Hoeven KH, Factor SM, Grober E, Aronson MK and Crystal HA. Hippocampal sclerosis: a common pathological feature of dementia in very old (> or = 80 years of age) humans. Acta Neuropathol 1994; 88: 212-221.
[169] Josephs KA and Dickson DW. Hippocampal sclerosis in tau-negative frontotemporal lobar degeneration. Neurobiol Aging 2006;
[170] Hatanpaa KJ, Blass DM, Pletnikova O, Crain BJ, Bigio EH, Hedreen JC, White CL, 3rd and Troncoso JC. Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia. Neurology 2004; 63: 538-542.
[171] Lee EB, Lee VM, Trojanowski JQ and Neumann M. TDP-43 immunoreactivity in anoxic, ischemic and neoplastic lesions of the central nervous system. Acta Neuropathol 2008; 115: 305-311.
[172] Zarow C, Sitzer TE and Chui HC. Understanding hippocampal sclerosis in the elderly: epidemiology, characterization, and diagnostic issues. Curr Neurol Neurosci Rep 2008; 8: 363-370.
[173] Zhang YJ, Xu YF, Dickey CA, Buratti E, Baralle F, Bailey R, Pickering-Brown S, Dickson D and Petrucelli L. Progranulin mediates caspase-dependent cleavage of TAR DNA binding protein-43. J Neurosci 2007; 27: 10530-10534.
[174] Dix MM, Simon GM and Cravatt BF. Global mapping of the topography and magnitude of proteolytic events in apoptosis. Cell 2008; 134: 679-691.
[175] Hasegawa M, Arai T, Nonaka T, Kametani F, Yoshida M, Hashizume Y, Beach TG, Buratti E, Baralle F, Morita M, Nakano I, Oda T, Tsuchiya K and Akiyama H. Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyo-trophic lateral sclerosis. Ann Neurol 2008; 64: 60-70.
[176] Zhang YJ, Xu YF, Cook C, Gendron TF, Roettges P, Link CD, Lin WL, Tong J, Castanedes-Casey M, Ash P, Gass J, Rangachari V, Buratti E, Baralle F, Golde TE, Dickson DW and Petrucelli L. Aberrant cleavage of TDP-43 enhances aggregation and cellular toxicity. Proc Natl Acad Sci U S A 2009; 106: 7607-7612.
[177] Lin WL and Dickson DW. Ultrastructural localization of TDP-43 in filamentous neuronal inclusions in various neurodegenerative diseases. Acta Neuropathol 2008; 116: 205-213.
[178] Dickson DW. TDP-43 immunoreactivity in neurodegenerative disorders: disease versus mechanism specificity. Acta Neuropathol 2008; 115: 147-149.
[179] Hutton M. Missense and splice site mutations in tau associated with FTDP-17: multiple pathogenic mechanisms. Neurology 2001; 56: S21-25.
[180] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E and Hutton M. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Hum Mol Genet 1999; 8: 711-715.
[181] Maraganore DM, de Andrade M, Elbaz A, Farrer MJ, Ioannidis JP, Kruger R, Rocca WA, Schneider NK, Lesnick TG, Lincoln SJ, Hulihan MM, Aasly JO, Ashizawa T, Chartier-Harlin

MC, Checkoway H, Ferrarese C, Hadjigeorgiou G, Hattori N, Kawakami H, Lambert JC, Lynch T, Mellick GD, Papapetropoulos S, Parsian A, Quattrone A, Riess O, Tan EK and Van Broeckhoven C. Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. Jama 2006; 296: 661-670.

[182] Rademakers R, Eriksen JL, Baker M, Robinson T, Ahmed Z, Lincoln SJ, Finch N, Rutherford NJ, Crook RJ, Josephs KA, Boeve BF, Knopman DS, Petersen RC, Parisi JE, Caselli RJ, Wszolek ZK, Uitti RJ, Feldman H, Hutton ML, Mackenzie IR, Graff-Radford NR and Dickson DW. Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia. Hum Mol Genet 2008; 17: 3631-3642.