Review Article

Neuropathology of non-Alzheimer degenerative disorders

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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 neurodegenerative 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
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<table>
<thead>
<tr>
<th>Amyloidoses</th>
<th>Disorder</th>
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<th>Major clinical feature</th>
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<tr>
<td>Aβ</td>
<td>Alzheimer disease</td>
<td>Corticolimbic</td>
<td>Dementia</td>
</tr>
<tr>
<td>Aβ</td>
<td>Familial British dementia</td>
<td>Corticolimbic &amp; cerebellar</td>
<td>Dementia &amp; ataxia</td>
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<tr>
<td>PrP</td>
<td>Creutzfeldt-Jakob disease</td>
<td>Cortical &amp; basal ganglia</td>
<td>Dementia &amp; movement disorder</td>
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<tr>
<td></td>
<td>Gerstmann-Straussler-Scheinker</td>
<td>Cortical &amp; Cerebellar</td>
<td>Ataxia &amp; dementia</td>
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| Tauopathies            | 4R                              | Basal ganglia & brainstem       | Parkinsonism                                  |
|                        | Corticobasal degeneration       | Cortical & basal ganglia        | Focal cortical syndrome & parkinsonism        |
|                        | Argyrophilic grain disease      | Limbic                         | Amnestic cognitive impairment                 |
|                        | 3R                              | Corticolimbic                   | Dementia & focal cortical syndromes           |
|                        | 3R+4R                           | 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          |

The amyloid deposits are sometimes referred to as beta-amyloidosis 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...
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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 PrPres) 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 neurodegenerative 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].

Figure 1. Amyloidoses: Familial British dementia (a) and familial Creutzfeldt-Jakob disease (b) have cerebellar amyloid deposits composed of non-Aβ amyloid, ABri and PrP.
**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 degeneration (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 lobe 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 lobe 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).
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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 and 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 convexty 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
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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 immunoreactive 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).
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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 heterogeneous nuclear ribonucleoproteins, 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...
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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].

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 pleomorphic TDP-43 neuronal inclusions and short curvilinear neurites in the same superficial layers (Figure 5b). The dentate fascia neurons are affected and have crescent shaped or round

Figure 4. TDP-43 ALS: Both skein-like (a) and Lewy-like hyaline inclusions (b) are positive for TDP-43.
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Table 2. Classification of frontotemporal lobar degenerations (adapted from [152])

<table>
<thead>
<tr>
<th>FTLD-Molecular abnormality</th>
<th>Genetic loci</th>
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<tbody>
<tr>
<td>FTLD-TDP</td>
<td></td>
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<tr>
<td>Frontotemporal lobar degeneration with TDP-43 inclusions</td>
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<tr>
<td>Subtype 1 (associated with SD)</td>
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<tr>
<td>Subtype 2 (associated with MND)</td>
<td>Chromosome 9</td>
</tr>
<tr>
<td>Subtype 3 (associated with FTDbv and PNFA)</td>
<td>GRN</td>
</tr>
<tr>
<td>Subtype 4 (associated with Paget’s and IBM)</td>
<td>VCP</td>
</tr>
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<td>FTLD-TAU</td>
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<td>Frontotemporal lobar degeneration with tauopathy</td>
<td>MAFT</td>
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<td>Pick’s disease (3R tauopathy)</td>
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<tr>
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<td>Frontotemporal lobar degeneration with intermediate filament inclusions</td>
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<tr>
<td>FTLD-UPS</td>
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<td>Frontotemporal lobar degeneration with inclusions composed of ubiquitin and other components of ubiquitin-proteasome system (e.g., P62-sequestosome)</td>
<td>CHMP2b</td>
</tr>
<tr>
<td>FTLD-AS</td>
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<td>Frontotemporal lobar degeneration with inclusions composed of α-synuclein (atypical Pick’s disease)</td>
<td>SNCA?</td>
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<td>FTLD-NI</td>
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<td>Frontotemporal lobar degeneration with no inclusions</td>
<td>None known</td>
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</table>

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 histopathologic 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.
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 to 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

**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 to 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 (HpScI)**

Hippocampal sclerosis (HpScI) 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 HpScI [169]. Conversely, in studies of HpScI, up to 12% of cases have ubiquitin-immunoreactive inclusions similar to FTLD-U [170]. Due to this strong association, when HpScI is detected, it is important to rule out FTLD-U. In our series of HpScI 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 HpScI 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 HpScI may be a forme fruste of FTLD-TDP. It is important to emphasize that HpScI 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 HpScI, 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 non-genetic risk factors and if there are common mechanisms for selective neuronal vulnerability that is the defining feature of these disorders.

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