Review paper

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Incidence and morphology of secondary TDP-43 proteinopathies: Part 1

Albert Acewicz[1], Tomasz Stępień[1], Paulina Felczak[1], Sylwia Tarka[2], Teresa Wierzba-Bobrowicz[1]

[1]Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland, [2]Department of Forensic Medicine, Medical University of Warsaw, Warsaw, Poland

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Abstract

Transactive response DNA binding protein of 43 kDa (TDP-43) is considered to play an essential role in the pathogenesis of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Growing body of evidence indicate that pathological TDP-43 inclusions frequently occur in the context of other distinctive hallmark pathologies, referred to as secondary TDP-43 proteinopathies. Comorbid TDP-43 pathology is well-documented in several neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, multiple system atrophy, or progressive supranuclear palsy. It may also appear as a consequence of less obvious disease etiologies, i.e. post-traumatic (chronic traumatic encephalopathy), neoplastic (pilocytic astrocytoma), or post-infectious (post-encephalitic parkinsonism). The aim of the present review was to evaluate the incidence, morphology, and role of TDP-43 pathology in the secondary TDP-43 proteinopathies. This article (Part 1) discussed TDP-43 pathology in more common neurodegenerative diseases, including Alzheimer's disease, Lewy body disease, Huntington's disease, multiple system atrophy, corticobasal degeneration, and progressive supranuclear palsy. A follow-up article (Part 2) will describe abnormal TDP-43 changes in rare neurodegenerative diseases or neurological diseases with nondegenerative etiology.

Key words: *TDP-43, pathology, proteinopathy, neurodegenerative, morphology, incidence, comorbidity.*

Introduction

In 2006, transactivation response (TAR) DNA binding protein 43 kDa (TDP-43) has been identified as a major component of ubiquitin-positive neuronal cytoplasmic aggregates in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS), and by now is considered to play an essential role in their pathogenesis [3]. Further reports showed that TDP-43-positive inclusions may be present in other neurodegenerative diseases with distinct pathological mechanisms, including Alzheimer's disease (AD), Lewy body disease (LBD), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), progressive supranuclear palsy (PSP), or multiple system atrophy (MSA), suggesting wider pathological role in neurodegeneration than initially thought [14,52]. In contrast to brain and spinal cord regions affected in FTLD and ALS, TDP-43 aggregates in other disorders have been predominantly observed in the limbic system, including hippocampus, amygdala, and adjacent cortices, indicating that TDP-43 pathology may involve distinct molecular processes [14]. Furthermore, presence and severity of abnormal proteins seems to be associated with incidence and pathobiology of other pathological proteins, potentially due to synergistic interactions, as shown for tau, α-synuclein, and TDP-43 [52]. Thus, overlap of distinct neuropathological processes frequently leads to a greater

Communicating author:

Albert Acewicz, MD, PhD, Department of Neuropathology, Institute of Psychiatry and Neurology, 9 Sobieskiego St., 02-957 Warsaw, Poland, e-mail: aacewicz@ipin.edu.pl

brain atrophy, more severe clinical presentations, and faster disease progression, suggesting the importance of co-pathologies in ante-mortem diagnosing and treatment [52].

The term 'proteinopathy' refers to a neurodegenerative disorders characterized by the accumulation of specific proteins in the central nervous system (CNS). In TDP-43 proteinopathies abnormal TDP-43 protein aggregates in neurons or oligodendroglia/astrocytes, and are usually associated with ageing and neurodegeneration [14]. 'Primary TDP-43 proteinopathy' refers to diseases, in which abnormal TDP-43 protein is a major and common pathology, and is responsible by location to the core disease symptoms. When TDP-43 pathology occurs in the context of distinctive hallmark pathology of the neurodegenerative disease, we could use a term of 'secondary proteinopathy' [14]. The aim of the present review was to evaluate the incidence, morphology, and role of TDP-43 pathology in CNS diseases with other major pathologies, referred to as secondary TDP-43 proteinopathies.

Pathology of TDP-43 protein

TDP-43 is a highly conserved RNA/DNA-binding protein belonging to the heterogeneous nuclear ribonucleoprotein family, encoded by *TARDBP* gene on chromosome 1p36 [14]. It consists of 414 amino acids with a molecular mass of 44.740 Da, and plays an important role in multiple cellular functions, including regulation of RNA splicing, stability, maturation and trafficking, modulation of microRNA biogenesis, and formation or regulation of stress granules [14]. TDP-43 is physiologically detected in the nucleus as diffuse staining; under pathological conditions it can form neuronal cytoplasmic inclusions (NCIs) (speckles, skeins, or tangles), neuronal nuclear inclusions (NNIs), dystrophic neurites (DNs), glial cytoplasmic inclusions (GCIs), perivascular astrocytic inclusions (PVIs), neuropil inclusions (NIs), and axonal spheroids (Fig. 1) [5]. Therefore, 'TDP-43 pathology' refers to loss of normal nuclear TDP-43 immunoreactivity, with TDP-43 protein 'inclusion bodies' in the neuronal cytoplasm as well as abnormal TDP-43 accumulation (mostly phosphorylated) in nuclei and neurites of neurons and/or oligodendroglia and astrocytes [47]. Based on FTLD immunohistochemistry, pathological TDP-43 morphology can be divided into four basic subtypes: type A has numerous NCIs and DNs; type B include numerous NCIs with few DNs; type C is characterized by longer and thicker DNs, with few NCIs; and type D has numerous NNIs and DNs, with few NCIs [5]. Ultrastructural studies revealed that TDP-43-positive structures are morphologically heterogeneous; in FTLD predominantly characterized by bundles of 10-20 nm diameter straight filaments with electron dense granular material within NCIs, NNIs, and DNs, less frequently by 10-17 nm diameter straight filaments without granular material within inclusions in neuritic processes [39]. The mechanisms of TDP-43-induced neurodegeneration are still not fully understood, although several mechanisms seem to be more or less involved at different stages of pathological process, including phosphorylation, ubiquitination, acetylation, autophagy, poly ADP-ribosylation, cystein oxidation, mitochondrial impairment, or stress granules formation (see review by de Boer *et al*. [14]).

TDP-43 is a major pathological hallmark of ALS and FTLD, detected in neuronal cytoplasmic inclusions of about 97% ALS and 50% FTLD subjects [62]. It is observed in up to 90% of hippocampal sclerosis (HS) cases, a common neuropathological entity defined by severe pyramidal cell loss and gliosis in CA1 and subiculum [1,44,48]. HS was initially associated with hypoxic/ischemic injury and epilepsy, although more recently, it has been primarily related with dementia in elderly persons. Abnormal TDP-43 inclusions appear to be a dominant pathology in Perry disease and facial onset sensory and motor neuronopathy (FOSMN), rare neurodegenerative disorders characterized by levodopa-resistant parkinsonism, depression/apathy, central hypoventilation, weight loss, and late-onset asymmetric facial numbness, facial weakness, bulbar palsy, respectively [17,53]. More recently, new neuropathological entity with dominant TDP-43 pathology has been established, named 'limbic-predominant age-related TDP-43 encephalopathy (LATE)' [47]. LATE is common in older adults (> 80-year-old), clinically characterized by an amnestic dementia syndrome similar to AD, and pathologically by TDP-43 inclusions spreading from amygdala to other limbic, cortical, and subcortical regions [47]. Interestingly, both TDP-43 aggregates and LATE neuropathological changes were observed in up to 40% of cognitively unimpaired elderly individuals [46,47,70].

Secondary TDP-43 proteinopathies

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease, most common cause of dementia, and one of the leading causes of mortality worldwide. Pathological hallmarks include neuritic plaques (extracellular deposits of amyloid β protein) and neurofibrillary tangles (NFTs) (intraneuronal deposits of tau protein), predominantly in the hippocampal and temporal regions, leading to notable reduction of brain cortical volume [55]. Growing body of evidence indicate that the majority of AD patients have additional pathological changes, which contribute to clinical presentation and disease progression [52]. Several studies using different research methods among various

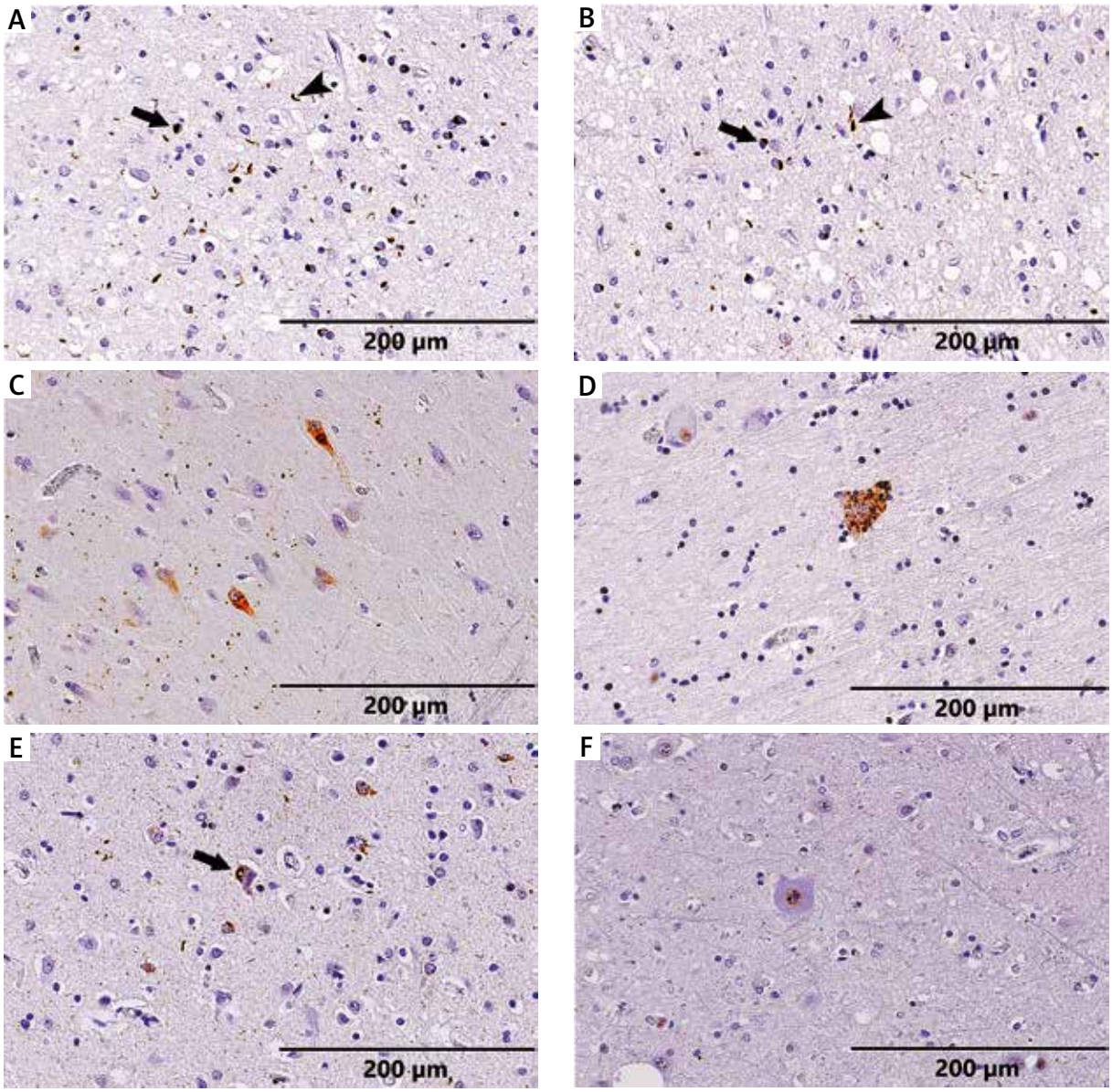

Fig. 1. Morphological forms of TDP-43 proteinopathy as showed by immunohistochemistry. TDP-43-positive, compact glial cytoplasmic inclusions (GCIs, arrow) and dystrophic neurites (DNs, arrowhead) in the frontal lobe of 68-year-old man with frontotemporal dementia (**A, B**). Diffuse, granular (**C**), and numerous, dense, globular (**D**) TDP-43-immunoreactive neuronal cytoplasmic inclusions (NCIs) in the temporal cortex of frontotemporal dementia patient (68 years, male). Skein-like NCIs (**E**, arrow) and dense, globular neuronal nuclear cytoplasmic inclusions (NNIs) (**F**) in the cervical spinal cord of 64-year-old woman with of amyotrophic lateral sclerosis. Paraffin-embedded tissue samples used for immunostaining were obtained from the archive of the Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland. The antibody used was phospho-TDP-43 (Ser409/410) (1 : 2000, Invitrogen, Waltham, USA).

cohorts, reported prevalence of TDP-43 inclusions in AD brains ranging from 20% to 74% [1,4,6,8,12,24-26, 28-31,33,43,50,52,69,70,72]. More specifically, LATE neuropathological changes were estimated on up to 60% in recent studies [7,32]. When comparing with other co-pathologies, i.e. infarcts, arteriolosclerosis, LBD, or HS, TDP-43 co-pathology was the most common comorbid pathology in AD [25]. Moreover, the burden of TDP-43 accumulation was observed to correlate with progression of AD, including faster and

greater brain atrophy, reduction of hippocampal cortex as well as more severe and rapid cognitive and global functioning impairment [9,11,12,15,25-27,29-32, 44,66,69].

Age, genetic risk factors, and comorbid pathologies seem to affect the incidence and severity of TDP-43 proteinopathy in AD. TDP-43 pathology is more common in late onset AD, when compared to familial AD, early onset AD or Down' syndrome; abnormal TDP-43 protein was identified in up to 14% of early onset AD, familial AD, and Down syndrome patients [12,41,43]. Comorbid co-pathologies increase the prevalence of TDP-43 accumulation in AD when compared with pure AD and control subjects [43,52]. It has been shown that apolipoprotein E (APOE) ε4 allele was an independent risk factor for TDP-43 pathology in patients with AD [73]. Some studies indicated that more severe AD neuropathological changes increase the incidence of TDP-43 accumulation, while others reported no differences in the prevalence of TDP-43 proteinopathy between severe and mild AD [52,66]. Furthermore, there are conflicting results regarding the impact of comorbid HS on the incidence of TDP-43 proteinopathy in AD [16,31,42,43].

Pathological TDP-43 aggregates in AD are found predominantly in the form of NCIs, DNs, GCIs, and occasionally NNIs; some studies report that the majority of cases are type A, other type B (Table I) [4,23,29,31,33,70,72]. TDP-43 aggregates differ in their composition, ranging from various domination of non-phosphorylated full-length TDP-43, phosphorylated TDP-43 to phosphorylated C-terminals [1,23,68,72]. Ultrastructural studies revealed that TDP-43 deposits are composed of 10-17 nm diameter straight filaments with coating by electron dense granular material. Occasionally, they present as granular material in neurons that also have NFTs contained tau filaments, and rarely as aggregates of uncoated filaments in unmyelinated neurites [1,39]. The distribution of TDP-43 aggregates differ between AD and FTLD; amygdala appears to be initial, most frequent, and severe affected region in AD [6,23,24,72]. The progression of TDP-43 pathology follows a stereotypical pattern of deposition that has been reported and validated by Josephs *et al*. [28]: initially manifests in amygdala (stage I), followed by entorhinal cortex and/or subiculum (stage II), dentate gyrus and/or occipitotemporal cortex (stage III), insular cortex, basal forebrain, ventral striatum, and/or the inferior temporal cortex (stage IV), substantia nigra, midbrain tectum, and inferior olive (stage V), and finally, middle frontal cortex and/or basal ganglia (stage VI) (Table I). According to some authors, TDP-43 spreading across the stages from neurons to neurons takes place in a prion-like manner, most likely via cell to cell anterograde axonal transport, direct neuron to neuron transmission, or with the use of glial cells [28,49].

The exact role and origin of TDP-43 accumulation in AD are still unknown. Both amyloid β and tau could trigger or exacerbate TDP-43 pathology or vice versa, since correlations were observed between TDP-43 burden and amyloid β or tau pathologies in AD cases [6,59]. In AD animal models, deposits of amyloid β lead to increased expression, phosphorylation, cleavage, aggregation, and distribution of TDP-43, which can be prevented by amyloid β clearance [21,22]. On the other hand, TDP-43 nuclear depletion/overexpression increases inflammation, β-secretase activity, endosomal/lysosomal localization of amyloid precursor protein, production of amyloid β oligomers, reduction of amyloid β fibrillization, and plaque formation [13,21,37,57]. Preclinical studies showed that pathological TDP-43 increases tau aggregation, affects tau mRNA stability and translation of tau proteins available for phosphorylation, promotes misregulation of tau isoforms [13,19,20]. Therefore, it is possible that tau, amyloid β, and TDP-43 share a common pathophysiological background; both tau and TDP-43 aggregates may co-localize in the same neurons, and similar-specific kinases lead to the increased phosphorylation and deposition of tau and TDP-43, i.e. TTBK1/2 [1,6,38,72].

Lewy body disease

Lewy body disease (LBD) is a neuropathological entity characterized by Lewy bodies and Lewy neurites composed of α-synuclein in the nigrostriatal, limbic, and neocortex regions, frequently accompanied by AD-type pathology, including NFTs and neuritic plaques [2]. LBD has a wide range of clinical presentations, including Parkinson's disease (PD), Parkinson's disease with dementia (PDD), and dementia with Lewy bodies (DLB) [2]. Cardinal symptoms of PD include tremor, postural instability, bradykinesia, and rigidity, and DLB cognitive impairment with fluctuations, parkinsonism, recurrent visual hallucinations, and rapid eye movement sleep behavior disorder (RBD). Several studies have demonstrated that TDP-43 pathology was relatively common in LBD, with the estimated frequency ranging from 16% to 73% [2,10,52,70,74]. More specifically, TDP-43 pathology was reported in 7-24% PD, 9-19% PDD, 25-67% DLB cases, and was more frequent when comorbid AD pathology occurred [4,23,33,43,45,74]. TDP-43 aggregates are predominantly observed in the form of NCIs, DNs and GCIs, largely confined to amygdala and hippocampus, less frequently widespread to entorhinal and temporal cortices, and type A is the most frequent morphological subtype (Table I) [2,4,23,43,45,70,74]. Morphology and anatomical distribution of TDP inclusions are similar to that observed

in AD, differ from FTLD by sparing frontal cortex and basal ganglia [4,23,43]. The presence of TDP-43 pathology seems to be associated with the severity of α-synuclein and tau pathology, though TDP-43 occasionally co-localize with α-synuclein in Lewy bodies or tau in NFTs in the same LBD neurons [4,23,45,70,74]. Thus, it has been showed that the co-expression of TDP-43 and α-synuclein exacerbates dopaminergic neuron loss in transgenic mice, and potentiates many behavioral, biochemical, and neuropathological deficits in Caenorhabditis elegans [56,67]. However, no clear correlation was found between TDP-43 pathology and clinical phenotypes of LBD, dementia in PDD, and clinical phenotype, age, sex, α-synuclein burden, and neuropathological stages of DLB [4,23,52,58,74].

Furthermore, LATE was recently reported in 21% of LBD cases (vs. 43% LBD + AD, 34% AD), with different neuropathological features when compared with AD (mostly NCIs in CA3, abundant fine neurites composed of C-terminal in CA2 to subiculum, earlier spread to dentate gurus and brainstem), and was associated with LBD subtype (diffuse/neocortical > transitional/limbic > brainstem), cognitive impairment, comorbid AD pathology, and genetic variants of *TMEM106B* and *GRN* [7,71]. LATE pathological changes in LBD seem to spread in stereotypical manner, from the amygdala and the periamygdaloid cortex (stage I) to the dentate gyrus, CA, subiculum, and entorhinal cortex (stage II), then to the brainstem and the cingulate gyrus (stage III), and finally to the orbitofrontal cortex, thalamus, lentiform nucleus, temporal lobes, frontal lobes, and angular gyrus (stage IV) [71].

Multiple system atrophy

Multiple system atrophy (MSA) is a rapidly progressive neurodegenerative disease, clinically characterized by variable combinations of parkinsonism, cerebellar ataxia, autonomic dysfunction, and pyramidal symptoms. Neuropathological features are pathognomonic oligodendrocytic GCIs containing α-synuclein, neuronal loss, and astrogliosis, predominantly in the striatonigral and the olivopontocerebellar system [35]. TDP-43 pathology has been found in up to 13% of MSA patients, although the

Table I. Neurological disorders with concomitant TDP-43 pathology

Neuropathological diagnosis	Dominant pathology	Group samples (range)	Incidence of TDP-43 pathology	Localization and distribution of TDP-43 pathology	Type of TDP-43 pathology	References
Alzheimer's disease	Tau aggregation (NFTs, neuropil threads), amyloid-β deposits (neuritic plaques)	12-342	20-74%	Amygdala (stage I), entorhinal cortex and/or subiculum (stage II), dentate gyrus and/or occipitotemporal cortex (stage III), insular cortex, basal forebrain, ventral striatum, and/or inferior temporal cortex (stage IV), substantia nigra, midbrain tectum, inferior olive (stage V), middle frontal cortex and/ or basal ganglia (stage VI)	NCIs, DNs, GCIs, occasionally NNIs	[1,4,6,8,12,24,26,28, 31,33,43, 50, 52,69, 70,72]
Lewy body disease	α-synuclein aggregation (Lewy bodies, Lewy neurites)	5-669	16-73% (PD: 7-24%, PDD: 9-19%, DLB: 25-67%)	Amygdala, hippocampus, less frequently entorhinal and temporal cortex	NCIs, DNs, GCIs	[2,4,10,23, 33,43, 45,52, 70,74]
Multiple system atrophy	α-synuclein aggregation (GCIs)	4-186	0-13%	Medial temporal lobe, less frequently subcortical structures, brainstem	DNs, PVIs, less frequently NCIs, GCIs	[18,33,35,52]
Progressive supranuclear palsy	Tau aggregation (tufted astrocytes, NFTs, coiled bodies)	5-945	0-26%	Amygdala (stage I), hippocampus, entorhinal cortex, dentate gyrus (stage II), medial occipitotemporal gyrus (stage III), middle frontal gyrus (stage IV)	NCIs, GCIs, DNs	[33,36,51, 52,72,75]
Corticobasal degeneration	Tau aggregation (corticobasal bodies, astrocytic plaques, coiled bodies)	3-187	9-45%	Brainstem, subthalamic nucleus, hypothalamus, thalamus, temporal cortex, frontal cortex	NCIs, DNs, GCIs	[33,34,51, 52,72,75]
Huntington's disease	Huntingtin aggregation (NNIs, NCIs, DNs)	2-15	0-100%	Cortex, adjacent white matter, striatum	DNs, NCIs	[33,54,61]

NFTs – neurofibrillary tangles, NCIs – neuronal cytoplasmic inclusions, PVIs – perivascular astrocytic inclusions, GCIs – glial cytoplasmic inclusions, DNs – dystrophic neurites, NNIs – neuronal nuclear inclusions, PD – Parkinson's disease, PDD – Parkinson's disease dementia, DLB – dementia with Lewy bodies

extent and severity were minimal in most cases [18, 33,35,52]. TDP-43 aggregates in the form of DNs and PVIs, less frequently as subpial astrocytic inclusions, NCIs and GCIs, located predominantly in the medial temporal lobe, rarely widespread in the subcortical structures and brainstem (Table I) [18,35]. There are conflicting results regarding co-localization of TDP-43 and α-synuclein aggregates; some studies reported that α-synuclein and TDP-43 occasionally occur in GCIs as granule-coated filaments within thalamic fasciculus, mammillothalamic tract, and paracentral cortex; others did not find any co-localization in GCIs [18,35]. A study of Koga *et al*. [35] failed to show any associations between risk variants of *TMEM106B* or *GRN* and TDP-43 pathology as well as convincing impact of TDP-43 aggregates on clinical manifestations in MSA. Only advanced age was found to be an independent risk factor for TDP-43 proteinopathy in MSA.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is pathologically characterized by extensive degeneration of the globus pallidus, subthalamic nucleus, substantia nigra, and pons, with neuronal/glial abnormal accumulation of tau in the form of tufted astrocytes, globose NFTs, and coiled bodies [36]. Broad clinical phenotypes include dystonic posturing of the neck, axial rigidity, vertical supranuclear gaze palsy, postural instability, gait disturbance, early falls, dysarthria, dysphagia, behavioral changes, executive dysfunction, and pseudo-bulbar palsy. Several studies revealed concomitant TDP-43 pathology in up to 26% PSP cases [33,36,51,52,72,75]. TDP-43 aggregates occur as NCIs, GCIs, and short DNs, most frequent and severe in the limbic system and temporal lobes (amygdala, hippocampus, and entorhinal cortex), but also in PSP-vulnerable regions (subthalamic nucleus, substantia nigra, and pontine tegmentum), and frequently co-localize with tau in the amygdala [36,75]. Koga *et al*. [36] identified four stages of TDP-43 pathology in PSP: TDP-43 aggregates only in the amygdala (stage I), additional involvement of the hippocampus, entorhinal cortex, and dentate gyrus (stage II), medial occipitotemporal gyrus (stage III), and extensive pathology in the middle frontal gyrus (stage IV) (Table I). Progression pattern of TDP-43 deposits closely resembles that seen in AD, with involvement of basal ganglia and PSP-vulnerable regions as a major difference between AD and PSP [28,36]. Age and comorbid HS, AD, AGD pathology are the strongest risk factors of TDP-43 pathology in PSP [36,75]. PSP cases with TDP-43 pathology have higher frequency of cognitive impairment and regional tau burden than TDP-43-negative PSP; although it is likely driven by concomitant pathology (AD or HS) [36,75]. Furthermore, no differences were found in *TMEM106B*, *GRN*, and *MAPT* frequencies between PSP with or without TDP-43 pathology [36].

Corticobasal degeneration

Corticobasal degeneration (CBD) is a neurodegenerative disease with numerous tau-positive neuronal and glial pathological lesions (corticobasal bodies, astrocytic plaques, coiled bodies), balooned neurons in gray and white matter of the neocortex, basal ganglia, diencephalon, and brainstem [34]. Classical symptoms include asymmetric apraxia, parkinsonism, dystonia, myoclonus, alien limb phenomena, cortical sensory loss, and cognitive dysfunction. Several studies estimated the frequency of TDP-43 pathology in CBD cases ranging between 9% and 45% [33,34,51,52,72,75]. Koga *et al*. [34] investigated various brain regions for TDP-43 pathology in 187 autopsy-confirmed CBD cases, and revealed that the brainstem (midbrain tegmentum) and subcortical nuclei (subthalamic nucleus, hypothalamus, thalamus) were the most frequently affected brain regions, NCIs, DNs, and GCIs were the most common morphological subtypes, and more severe TDP-pathology was associated with predominant clinical diagnosis of PSP and low frequency of *MAPT* H1 haplotype (Table I). Furthermore, Uryu *et al*. [72] showed that in CBD widespread TDP-43 staining pattern, including temporal and frontal cortex and basal ganglia, was more frequent than restricted to limbic and hippocampal regions, and there was an unique, predominantly glial TDP-43 pathology, with staining of astrocytic plaque-like structures and coiled bodies. Although, the presence of TDP-43 pathology seems to correlate with the severity of tau burden in the olivopontocerebellar system, no obvious correlation was found between TDP-43 pathology and CBD clinical course and phenotype [34,40,72]. On the other hand, there are single case studies in the literature reporting that widespread, asymmetric TDP-43 rather than symmetric tau pathology contributes to the laterality of degeneration in CBD [63,64].

Huntington's disease

Huntington's disease (HD) is caused by expanded CAG trinucleotide repeat mutation in the gene coding for huntingtin and clinically characterized by progressive involuntary choreiform movements, psychiatric disturbances, and cognitive decline [54]. In neuropathological examination, general shrinkage of the brain and massive neuronal degeneration of the striatum are observed, with aggregates of abnormal huntingtin in neuronal nuclei, and to a lesser extent, in the cytoplasm and dendrites [54]. Schwab *et al*. [54] revealed that in 10 autopsied HD cases, TDP-43 frequently co-localized with

huntingtin in DNs and NCIs, but not in NNIs, with similar shape and distribution to huntingtin and ubiquitin inclusions (Table I). Similarly, widespread huntingtin- and TDP-43-positive inclusions were found in CNS of 2 HD cases that developed ALS in later life, with partial overlapped regional distributions, and occasional co-extistance inside the same neurons (but not co-localize within the same inclusions) [61]. On the other hand, King *et al*. [33] did not find TDP-43 pathological changes in five examined HD cases. Biochemical studies confirmed increased expression, oligomerization, and aggregation of TDP-43 in the putamen of autopsied HD samples [60]. Furthermore, in a transgenic worm model, genetic loss of function mutations for nematode orthologues of TDP-43 was shown to reduce mutant huntingtin-induced neurodegeneration and behavioral defects [65].

Conclusions

Pathological TDP-43 aggregates are a common, concomitant, and prominent pathological features in a wide range of neurodegenerative disorders, including AD, LBD, CBD, PSP, HD, and overlap in neuropathological processes with several abnormal proteins, including tau, α-synuclein, amyloid β, and huntingtin (Table I) [52]. Pathological TDP-43 protein predominantly forms NCIs and DNs confined to limbic and temporal regions, and follows a stereotypical pattern of progression to the basal ganglia, midbrain, and frontal cortex [28,52]. Dominant pathology frequently affects TDP-43 co-pathology prevalence and severity; the more severe primary pathology or more co-pathologies, the incidence of TDP-43 pathology increase [52]. Similarly, TDP-43 is involved in formation and spreading of other pathological proteins [13,19-22,37,57]. Overlap of distinct pathological mechanisms is frequently associated with greater brain atrophy, faster disease progression, and more severe clinical phenotype [15,27,66]. Although, strong relationship between TDP-43, age, and cognitive decline was established, TDP-43 inclusions were observed in up to 40% of cognitively normal elderly individuals [46,47,70]. Therefore, the co-existence of distinct pathologies with TDP-43 could be interpreted in two ways. First, the presence of TDP-43 is secondary to the dominant pathology and shares overlapping features with main disease. Second, TDP-43 pathology represents an equal phenomenon derived from the common causative factor with other pathological proteins.

Disclosure

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