Review paper

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Incidence and morphology of secondary TDP-43 proteinopathies: Part 2

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Abstract

Transactivation (TAR) DNA binding protein 43 kDa (TDP-43) inclusions frequently occur as a comorbid pathology in several neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Lewy body disease, and progressive supranuclear palsy, and may appear in association with nondegenerative neurological etiology, for example neoplastic, paraneoplastic, traumatic, or infectious. Relationships between various pathological proteins and mechanisms associated with TDP-43-induced neurodegeneration are still not fully understood. Thus, overlap of distinct neuropathological mechanisms frequently leads to greater brain atrophy and a more severe clinical course, suggesting the importance of co-pathologies in ante-mortem diagnosing and treatment. The present review aims to discuss the incidence, morphology, and role of TDP-43 pathology in the context of other dominant, hallmark pathologies, referred to as secondary TDP-43 proteinopathies. The previous part (Part 1) focused on common neurodegenerative diseases, including Alzheimer's disease, Huntington's disease, and Lewy body disease, while the present part (Part 2) discusses TDP-43 pathology in rare neurodegenerative diseases and neurological diseases with nondegenerative etiology.

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

Introduction

Transactivation (TAR) DNA binding protein 43 kDa (TDP-43) is considered to play an essential role in the pathogenesis of frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS), predominant age-related TDP-43 encephalopathy (LATE), hippocampal sclerosis (HS), Perry disease, and facial onset sensory and motor neuronopathy (FOSMN) [1,11]. Furthermore, pathological TDP-43 aggregates frequently occur in the context of other distinctive hallmark pathologies, referred to as "secondary TDP-43 proteinopathies". They are observed in up to 74% of patients with Alzheimer's disease (AD), 73% with Lewy body disease (LBD), 45% with corticobasal degeneration (CBD), 26% with progressive supranuclear palsy (PSP), and 13% with multiple system atrophy (MSA) [1]. More interestingly, abnormal TDP-43 may appear in association with nondegenerative neurological etiology, i.e. post-traumatic (chronic traumatic encephalopathy), neoplastic (pilocytic astrocytoma), post-infectious (post-encephalitic parkinsonism), and paraneoplastic (paraneoplastic lower motor neuron disease) [32,33,42,55].

TDP-43 is physiologically detected in the nucleus as diffuse staining; when misfolded it can form neuronal cytoplasmic inclusions (NCIs), neuronal nuclear inclusions (NNIs), dystrophic neurites (DNs), glial cytoplasmic inclusions (GCIs), perivascular astrocytic inclusions (PVIs), and axonal spheroids [1]. It is still unknown

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whether comorbid TDP-43 pathology shares a common etiological background, or represents a consequence of the primary pathological process in the pathogenesis of neurological diseases [1]. Thus, overlap of distinct neuropathological mechanisms frequently leads to greater brain atrophy and a more severe clinical course, suggesting the importance of co-pathologies in ante-mortem diagnosis and treatment [1].

The aim of the present review is to evaluate the incidence, morphology, and role of TDP-43 pathology in secondary TDP-43 proteinopathies. The previous part (Part 1) focused on common neurodegenerative diseases, including AD, Huntington's disease (HD), PSP, MSA, and LBD, while the present part (Part 2) discusses TDP-43 pathology in rare neurodegenerative diseases or neurological diseases with nondegenerative etiology [1].

Secondary TDP-43 proteinopathies

Spinocerebellar ataxias

Spinocerebellar ataxias (SCAs) are heterogeneous, hereditary, progressive groups of neurodegenerative diseases that predominantly affect the cerebellum. Most common types (SCA1, SCA2, SCA3) are inherited in an autosomal dominant manner and are caused by abnormal CAG-repeat expansion in the genes encoding disease-associated proteins, i.e. ataxin-1, ataxin-2, and ataxin-3 [61]. The cardinal neuropathological feature is olivopontocerebellar atrophy with neuronal loss, reactive gliosis, and ubiquitinated, polyglutamine-positive neuronal inclusions [61]. Seidel *et al*. [54] examined the brains of 7 patients with SCA3 and revealed widespread axonal aggregates in fiber tracts with a few TDP-43 positive axonal inclusions. In the study of Tan *et al*. [56] a few TDP-43-positive NCIs were found in the lower motor neurons of the brainstem and spinal cord of SCA3 cases (n = 10); NCIs were linear, wisp-like, skein-like, or rod-like bodies, indistinguishable in morphology from those seen in ALS and never co-localized with expanded polyglutamine stretches or ataxin-3. Toyoshima *et al*. [58] described a 52-year-old patient with SCA2 and widely distributed TDP-43-positive NCIs, NNIs, and GCIs in the central nervous system (CNS) except the lower motor neuron system; TDP-43 inclusions were present in small numbers in individual regions, sometimes co-existed with polyglutamine inclusions, but never co-localized in the same neurons. Similarly, a 56-year-old woman with SCA2 and mild TDP-43 pathology in the neocortex and hippocampus was reported by Bäumer *et al*. [5] (Table I). Preclinical studies showed that ataxin-2 can modify TDP-43 toxicity *in vitro* and *in vivo*; the interaction seems to be RNA dependent, and increased ataxin-2 expression can upset the balance of subcellular TDP-43 distribution, resulting in RNA dysregulation [13,47]. On the other hand, decreased expression of ataxin-2 in ALS mice reduces TDP-43 aggregation, markedly increasing mouse survival and motor functions [6].

Hereditary spastic paraplegias

Hereditary spastic paraplegias (HSPs) are heterogeneous neurodegenerative diseases, which include a large spectrum of inherited disorders presenting with lower limb spasticity as the common clinical feature. Main histopathological finding is atrophy of cervical and thoracic spinal cord with axonal degeneration involving the lateral corticospinal tracts [12,46]. Mori *et al*. [46] described two patients with spastic paraplegia (SPG) with thinning of the corpus callosum from different families (one with genetically diagnosed SPG11) and revealed widespread distribution of eosinophilic, TDP-43 and p62-positive NCIs. TDP-43-positive NCIs, GPIs, and DNs were observed in various regions of the CNS, i.e. spinal cord, striatum, substantia nigra, thalamus and occasionally co-localized with p62 aggregates. On the other hand, in the study of Denora *et al*. [12] two SPG11 patients showed motor neuron degeneration mimicking ALS with p62-positive inclusions and lipofuscin deposits in affected CNS regions without TDP-43 pathology. Furthermore, widespread spinal and cerebral TDP-43-positive skein-like and round NCIs have been reported in an SPG6 patient with mixed HSP and ALS phenotype (Table I) [39].

Chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease caused by repetitive and cumulative head trauma leading to psychiatric, behavioral, and cognition disturbances [43]. Pathological findings include generalized cortical atrophy and atrophy of the cavum septum pellucidum with multifocal, extensive, perivascular tau-positive neurofibrillary tangles (NFTs), astrocytic tangles, and neurites at the depths of the cortical sulci [43]. Several large clinicopathological series revealed that over a third of CTE cases shared comorbid pathology with one or more other neurodegenerative disorders, i.e. AD, PSP, FTLD and dementia with Lewy bodies (DLB) [41,42]. McKee *et al*. [42] reported that of 68 cases with a history of repetitive, mild traumatic brain injury and pathological diagnosis of CTE, 85% had coexisting TDP-43 pathology; TDP-43 was the most common comorbid pathology in comparison to other co-pathologies (vs. 11% of AD, 16% of LBD, 6% of FTLD cases) and partially co-localized with tau. In several small groups of football players and boxers with progressive cognitive impairment and pathological diagnosis of CTE, TDP-43 aggregates were identified in 75-100% of cases [29,35,40]. Furthermore, concomitant CTE and TDP-43 pathology was described

in several case reports of athletes with various clinical phenotypes, including AD, ALS, and PSP [19,34,64]. In the early stages of CTE, TDP-43 pathology consists of immunopositive DNs in the subcortical white matter and fornix (stage I), while in the later stages it additionally includes NCIs in the brainstem or medial temporal lobe (stage II), cerebral cortex (stage III), and finally severe and widely distributed rounded and thread-like DNs, GCIs, and NCIs in the cerebral cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem, and occasionally the spinal cord (stage IV) (Table I) [41]. Interestingly, in cases with the most severe TDP-43 deposition, TDP-43 inclusions are found in all layers of the neocortex and occasionally in the dentate fascia of the hippocampus, which is very similar to the distribution observed in FTLD [41]. Thus, it is possible that either tau pathology triggers the molecular pathways resulting in the accumulation of other protein pathologies or both tau, TDP-43 and other pathologies share common risk factors, notably repetitive head trauma and axonal injury. In line with the above, it has been found that both single and repetitive traumatic injury could trigger or exacerbate TDP-43 mislocalization, phosphorylation, neuronal death, and impaired cognition in cultured neurons and animal models [2,25,57].

Argyrophilic grain disease

Argyrophilic grain disease (AGD) is characterized by the presence of small, spindle or comma-shaped tau-immunopositive structures, called argyrophilic grains, within the dendrites of neurons in medial temporal and limbic regions [4,15]. No clear clinical syndrome has yet been identified; patients can present with progressive cognitive decline, as well as psychiatric manifestations, including mood disorders and personality changes [4,15]. Several studies have reported high frequency of TDP-43 pathology in AGD ranging from 54% to 60%; abnormal TDP-43 predominantly forms DNs, NCIs, and GCIs, and is found in the limbic and temporal regions (Table I) [4,15,59]. The distribution of TDP-43-positive structures is largely consistent with argyrophilic grains, although TDP-43 aggregates rarely co-localize with tau [4,15]. Fujishiro *et al*. [15] reported no differences in demographics, age at death, disease duration, brain weight, Braak neurofibrillary tangle stage, or severity of amyloid β burden between AGD cases with and without TDP-43 inclusions. On the other hand, Uchino *et al*. [59] found that mean age at death was higher in AGD with TDP-43 pathology than without.

Primary age-related tauopathy

Primary age-related tauopathy (PART) is a common pathological entity characterized by the presence of tau-positive NFTs with minimal to absent amyloid β pathology [27]. PART is associated with human ageing and can be asymptomatic or manifest as cognitive decline or dementia [26,27]. Several studies have shown that 29-100% of PART cases have TDP-43-positive aggregates [26-28,65]. NCIs are usually rare to scant, predominantly perivascular, most frequent in the amygdala, hippocampus, and associated with age, HS, Braak neurofibrillary tangle stage, amygdala, hippocampal, and cortical atrophy [26-28,65]. Four stages of sequential spread of TDP-43 in PART were reported, generally similar to early TDP-43 stages in AD, but tending to be more restricted to the limbic system: stage I characterized by the presence of TDP-43 lesions in the amygdala, stage II additionally in the hippocampus, stage III in the neocortex, and stage IV in the putamen, pallidum, and insular cortex (Table I) [65].

Pick's disease

Pick's disease (PiD) is a pathological entity characterized by frontal and temporal atrophy with neuronal loss, cortical gliosis, spongiosis, αβ-crystallin-positive ballooned neurons, and neuronal tau-positive Pick bodies [14]. Several studies did not detect TDP-43 pathology in small PiD groups [9,22,29,49,50,60]. However, Freeman *et al*. [14] reported that 5 of 15 PiD cases with Pick bodies and smaller intracytoplasmic inclusions showed staining for ubiquitin, tau, and TDP-43. Similarly, Arai *et al*. [3] noted that the number of TDP-43-positive Pick bodies was comparable to that of tau-positive ones in 7 PiD examined cases (Table I).

Neurodegeneration with brain iron accumulation

Neurodegeneration with brain iron accumulation type 1 (NBIA1), or more precisely pantothenate kinase-associated neurodegeneration (PKAN), is an autosomal recessive or sporadic neurodegenerative disorder caused by a loss of function of the pantothenate kinase 2 protein [63]. The clinical phenotype is characterized by early-onset dystonia, parkinsonism, dysarthria, cognitive impairment, and retinitis pigmentosa [63]. Neuropathological findings include "mummified" neurons, neuronal loss and gliosis, axonal degeneration (spheroid bodies), and iron accumulation in the pallidonigral system, with occasional α-synuclein-positive Lewy bodies and tau-positive NFTs [20,63]. Haraguchi *et al*. [20] described a 49-year-old woman with slowly progressive parkinsonism and dementia, with neuropathological findings typical for NBIA with concomitant tau- and TDP-43 pathology. Abundant tau-positive NFTs were found in the hippocampus, cerebral neocortex, basal ganglia, and brain stem and TDP-43-positive NCIs and GCIs in the hippocampus, frontal and temporal lobes, and basal ganglia (Table I).

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
Spinocerebellar ataxia type 3	Ataxin-3 aggregation (NNIs, NCIs, axonal inclusions)	7-10	100%	Brainstem, spinal cord (lower motor neuron)	GCIs, NCIs	[54,56]
Spinocerebellar ataxia type 2	Ataxin-2 aggregation (NCIs, NNIs)	Case report	n/a	Neocortex, hippocampus	NCIs, NNIs, GCIs	[5,58]
Spastic paraplegia type 11	Axonal degeneration	2	0-100%	Spinal cord, striatum, substantia nigra, thalamus	NCIs, GCIs, DNs	[12,46]
Spastic paraplegia type 6	Axonal degeneration	Case report	n/a	Spinal cord, substantia nigra, amygdala, entorhinal cortex, hippocampus, cingulate gyrus, basal ganglia, neocortex	NCIs, GCIs, NIs	[39]
Neurodegeneration with brain iron accumulation type 1	Iron accumulation, neuronal degeneration (spheroid bodies, "mummified" neurons)	Case report	n/a	Hippocampus, frontal cortex, temporal cortex, basal ganglia	NCIs, GCIs	[20]
Argyrophilic grain disease	Tau aggregation (argyrophilic grains)	11-15 Case report	54-60% n/a	Limbic and temporal regions	DNs, NCIs, GCIs	[4,15,59]
Chronic traumatic encephalopathy	Tau aggregation (NFTs, astrocytic tangles)	3-68 Case reports	75-100% n/a	Subcortical white matter, fornix (stage I), brainstem, medial temporal lobe (stage II), cerebral cortex (stage III), cerebral cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem, spinal cord (stage IV)	DNs, NCIs, GCIs	[19,29,34, 35,40-42, 64]
Pick's disease	Tau aggregation (Pick bodies)	2-15	0-100%	Dentate gyrus, amygdala, temporal, frontal cortex, white matter	NCIs, occasionally DNs, GCIs	[3,9,14,22, 29,49, 50,60]
Primary age-related tauopathy	Tau aggregation (NFTs)	16-116	29-100%	Amygdala (stage I), hippocampus (stage II), neocortex (stage III), putamen, pallidum, insular cortex (stage IV)	NCIs	[26-28,65]

Table I. Cont.

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
Down syndrome	Tau aggregation (NFTs, neuropil threads), amyloid-β deposits (neuritic plaques)	14-50	6-14%	Amygdala, hippocampus	NCIs, DNs, neuropil threads	[10,36]
Cockayne syndrome	Neuronal degeneration (dystrophic dendrites, spheroid bodies), glial degeneration (multinucleated astrocytes, bizarre astrocytes), axonal degeneration	Case report	n/a	Cerebellar cortex, inferior olivary nucleus, less frequently cerebellar white matter, subependymal regions, brain-stem, spinal cord	GCIs, NCIs	[51]
Alexander disease	GFAP aggregation (RFs)	7	57%	White matter, medulla oblongata, thoracic spinal cord	Inclusions in periphery of RFs	[62]
Post-encephalitic parkinsonism	Tau aggregation (NFTs)	7	57%	Amygdala, hippocampus, dentate gyrus, entorhinal cortex, temporal cortex	NCIs, DNs, rarely NNIs	[33]
Amyotrophic lateral sclerosis/ parkinsonism–dementia complex	Tau aggregation (NFTs)	2-39 Case report	100% n/a	Frontotemporal and limbic regions, hippocampus, spinal cord	NCIs, GCIs, DNs, NIIs, NFTs, CBs, tufted astrocytes, thorn-shaped astrocytes	[17,21,30, 38,44,45, 48]
Familial British dementia	Tau aggregation (NFTs), amyloid-β deposits (neuritic plaques)	5 Case report	20% n/a	Amygdala, hippocampus	NCIs, DNs	[31,53]
Niemann-Pick disease type C	Cholesterol accumulation (meganeurites, ectopic dendrites, swollen neurons), tau aggregation (NFTs, neuropil threads)	Case report	n/a	Cerebellum	NCIs, loss of nuclear staining	[8]
Neuronal ceroid lipofuscinosis type 11	Lipopigment accumulation (ballooned neurons), axonal degeneration	Case report	n/a	n/a	Occasionally loss of nuclear staining, immunoreactive ring around the nucleus	[23]
Pilocytic astrocytoma	Astrocytic glioma infiltration, RFs, granular bodies	5	100%	n/a	Inclusions in periphery of RFs and granular bodies	[32]
Paraneoplastic lower motor neuron disease with sensorimotor neuropathy	Inflammatory cells infiltrations (B cells)	Case report	n/a	Hypoglossal nuclei, spinal cord	NCIs, GCIs	[55]

NFTs – neurofibrillary tangles, RFs – Rosenthal fibers, NCIs – neuronal cytoplasmic inclusions, GCIs – glial cytoplasmic inclusions, DNs – dystrophic neurites, NNIs – neuronal nuclear inclusions, CBs – coiled bodies, n/a – not applicable/not available

Down syndrome

Down syndrome is the most common genomic disorder of intellectual disability, caused by trisomy of chromosome 21. It is associated with a high frequency of AD-dementia and pathology because of genetically determined over-production of amyloid β peptide [10]. Davidson *et al*. [10] investigated the temporal cortex and hippocampus of 50 individuals with Down syndrome and found that 6% of them had HS and TDP-43 pathology, 6% had only HS, while none had TDP-43 without HS. In the study of Lippa *et al*. [36] TDP-43 aggregates were found in 14% of patients with Down syndrome (n = 14), TDP-43 inclusions did not co-localize with NFTs and amyloid plaques, and the amygdala followed by the hippocampus were most commonly affected (Table I).

Alexander disease

Alexander disease is a rare neurodegenerative disorder caused by dominant mutations in the gene encoding glial fibrillary acidic protein (GFAP) with Rosenthal fibers (RFs), astrogliosis, and loss of myelin as a major pathological findings [62]. RFs are brightly eosinophilic, homogeneous structures of variable size and shape, formed within the cytoplasmic extensions of astrocytes, stain for GFAP, αβ-crystallin, 27 kDa heat-shock protein and ubiquitin and are generally indicative of a chronic reactive process [52]. Walker *et al*. [62] reported that TDP-43 is present and co-localizes with GFAP in Rosenthal fibers of Alexander disease brains, insoluble phosphorylated full-length and high molecular weight TDP-43 accumulates in the brain white matter, and the phosphorylation of TDP-43 correlates with age of disease onset and the level of GFAP pathology (Table I). Furthermore, phosphorylated TDP-43 co-localizes with GFAP in an age-dependent manner in the brains of knock-in mice which harbor a GFAP mutation and co-localize with Rosenthal fibers in wild-type GFAP-overexpressing mice. Interestingly, insoluble C-terminal fragments of TDP-43 were absent or barely detectable in Alexander disease tissue samples and pathological TDP-43 aggregates were limited exclusively to astrocytes and Rosenthal fibers, which may suggest that the presence of C-terminal fragments is not necessary for aberrant TDP-43 cytoplasmic localization, phosphorylation, or insolubility and there are differences in pathological TDP-43 processing in neurons compared with astrocytes.

Cockayne syndrome

Cockayne syndrome (CS) is a rare genetic disorder characterized by dwarfism, microcephaly, dysmorphism, retinitis pigmentosa, deafness, cutaneous photosensitivity, mental retardation, accelerated ageing, and pyramidal and cerebellar signs caused by recessive mutations in either the *ERCC6* gene (also known as *CSB*) or the *ERCC8* gene (also known as *CSA*) [51]. Sakurai *et al*. [51] described a CS patient with numerous astroglial TDP-43-positive structures and abundant RFs in post-mortem brain examination. Astrocytic, round TDP-43 inclusions were predominantly located in the cerebellar cortex and the inferior olivary nucleus, and to a lesser extent in the cerebellar white matter, subependymal regions in the brainstem, and spinal cord. NCIs were only observed in a small number of neurons of the inferior olivary nucleus (Table I).

Post-encephalitis parkinsonism

Post-encephalitic parkinsonism (PEP) is the most common sequela of the encephalitis lethargica global pandemic between 1915 and 1927 [16]. PEP is characterized by severe neuronal loss, gliosis, and tau-positive NFTs in the substantia nigra, subthalamic nucleus, brainstem nuclei, hippocampus, entorhinal cortex [16]. Ling *et al*. [33] examined 7 PEP brains and found that more than 50% of brains had TDP-43 pathology (NCIs and DNs, rarely NNIs), mostly restricted to the limbic region (Table I). However, there was no correlation between the presence TDP-43 aggregates and parkinsonism onset, disease duration, age of death, or HS.

BRI2 gene-related dementias

Familial British dementia (FBD) and familial Danish dementia (FDD), also known as *BRI2* gene-related dementias, are inherited diseases in which amyloid peptides, ABri in FBD and ADan in FDD, are cleaved from the C-terminus of the mutated BRI2 precursor proteins [31,53]. However, ABri and ADan show no homology to amyloid β; the clinical presentation and pathological changes in FBD and FDD are similar to those observed in AD, including amyloid plaques, CAA, and tau-positive NFTs [31,53]. Schwab *et al*. [53] reported a FBD case with TDP-43-positive NCIs, DNs, and occasional TDP-43 positivity in NFTs in the limbic region. Furthermore, Lashley *et al*. [31] examined five FBD and four FDD cases and found rare TDP-43-positive NCIs in the CA1 hippocampal subregion in only one FBD case (Table I). Pathological changes are similar in limbic structures of AD and FBD, which could indicate that related mechanisms are involved in TDP-43-induced neurodegeneration in both AD and FBD.

Amyotrophic lateral sclerosis/parkinsonism–dementia complex

Amyotrophic lateral sclerosis/parkinsonism–dementia complex (ALS/PDC) are endemic neurodegenerative disorders that have accumulated in the Kii Peninsula of

Japan and on the island of Guam and West Papua [45]. Several hypotheses have been suggested for the cause of ALS/PDC, notably genetic predisposition, environmental factors, and exposure to neurotoxins [45]. ALS/PDC are multiple proteinopathies characterized by neuronal loss and abundant NFTs composed of hyperphosphorylated tau, α-synuclein, and TDP-43 [44,45]. Some studies have shown similar frequency of tau, TDP-43 and α-synuclein inclusions in the ALS/PDC, while other reports indicate that severe tau pathologies dominate the pathological picture [17,44,45]. TDP-43 immunostains a subset of pathological neuronal and glial inclusions, i.e. NCIs, GCIs, DNs, NNIs, NFTs, coiled bodies, tufted astrocytes, thorn-shaped astrocytes, and skein-like inclusions, and they are predominantly located in frontotemporal, limbic, hippocampal, and spinal cord regions (Table I) [17,21,30,38,44,45,48]. Furthermore, double immunofluorescence studies revealed that TDP-43 sometimes co-localizes with tau in NFTs and coiled bodies in ALS/PDC patients [21,44,48].

Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinoses (NCLs/CLNs) are a clinically and genetically heterogeneous group of inherited lysosomal storage diseases that result from excessive accumulation of lipopigments in the body's tissues, i.e. skin, brain, and retina. Neuronal ceroid lipofuscinosis type 11 (CLN11) is caused by *GRN* mutations and characterized by cerebellar ataxia, myoclonus, retinitis pigmentosa, epilepsy, and progressive cognitive decline [18,23]. Assuming that identical *GRN* mutations underlie CLN11 and FTLD-TDP pathology, Götzl *et al*. [18] found that Grn(–/–) mice have pathobiochemical features of both *GRN*-associated FTLD-TDP and NCL/lysosomal impairment and Ctsd(–/–) mice (mouse model of NCL) have elevated brain levels of GRN, TMEM106B proteins and pathologically phosphorylated TDP-43. In patients with *GRN* mutations with early-onset CLN11 phenotype no TDP-43-positive NCIs were identified, but in some CLN11 neurons loss of normal nuclear TDP-43 staining was associated with an abnormally immunoreactive ring around the nucleus, and it was hypothesized that it represent the pre-inclusion stage of FTLD in young CLN11 patients (Table I) [23].

Niemann-Pick disease type C

Niemann-Pick type C (NPC) is an autosomal recessive lysosomal disease characterized by the accumulation of cholesterol in lysosomes and late endosomes due to mutations in the *NPC1* or *NPC2* gene [8,37]. Neuropathological features include meganeurite formation, ballooned neurons, extensive growth of ectopic dendrites, formation of tau-positive NFTs, neuroinflammation, neuronal loss, and neuroaxonal dystrophy [8,37]. Liu *et al*. [37] studied NPC mouse neuronal models and observed accumulation of cytoplasmic mislocalized TDP-43 protein in the distinct neuronal subtypes in association with nuclear membrane abnormalities and disruption of nucleocytoplasmic transport. Furthermore, Dardis *et al*. [8] documented altered TDP-43 expression and/or mislocalization in both mouse and human NPC neuronal models and diffuse, cytoplasmic TDP-43 immunostaining in Purkinje cells with concurrent loss of nuclear TDP43 in 61-year-old patient with NPC (Table I).

Pilocytic astrocytoma

Lee *et al*. [32] examined the TDP-43 immunostaining profile in various human brain tumors and observed TDP-43 cytoplasmic staining in cells in M-phase of the cell cycle in necrotic tumors of high malignancy, i.e. glioblastoma, medulloblastoma, diffuse large B cell lymphoma, and TDP-43 immunoreactivity in eosinophilic granular bodies and/or RFs in low grade or reactive lesions, i.e. pilocytic astrocytomas, reactive brain parenchyma adjacent to a craniopharyngioma, and the gliotic wall of a pineal cyst (Table I). Pilocytic astrocytoma is a common, low-grade, primary tumor in children and adolescents, characterized by compact bipolar cells and areas with microcysts, hyalinized vessels, RFs, and occasional eosinophilic granular bodies [52].

Paraneoplastic lower motor neuron disease with sensorimotor neuropathy

Suzuki *et al*. [55] described a case of a 77-year-old man with paraneoplastic lower motor neuron disease with sensorimotor neuropathy due to Waldenström's macroglobulinemia and found TDP-43-positive inclusions in the motor neurons and astrocytes of the hypoglossal nuclei and whole spinal cord (Table I). Thus, it is possible that TDP-43 secondarily accumulated due to immunological mechanisms, a paraneoplastic factor, or age, or occurred coincidentally.

Conclusions

Pathological TDP-43 aggregates have been found in several rare neurodegenerative diseases with various pathophysiological background, for example SCA2/3, NBIA1, FBD, NPC, CLN11, and Alexander disease (Table I). Interestingly, abnormal TDP-43 protein may be associated with nondegenerative disease etiology, i.e. neoplastic (pilocytic astrocytoma), traumatic (CTE), infectious (post-encephalic parkinsonism), paraneoplastic (paraneoplastic lower motor neuron disease) (Table I). On the other hand, TDP-43 inclusions were not found in prion diseases (Creutzfeldt-Jakob disease,

Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia), spinal and bulbar muscular atrophy, ischemic stroke, anoxic encephalopathy, and necrotic tumors [24,32,56]. Despite the different etiological background, most secondary TDP-43 proteinopathies demonstrate similar morphology and distribution; TDP-43 inclusions aggregate in the neuronal cytoplasm predominantly in limbic and temporal brain regions (Table I). Thus, the presence of TDP-43 inclusions may reflect either a common pathogenesis or a common response to the accumulation of proteinaceous process. Further large-group studies are needed to determine the role of TDP-43 in the context of other pathological conditions and translate discovered knowledge into clinical practice.

Disclosure

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