Review

Secondary Protein Aggregates in Neurodegenerative Diseases: Almost the Rule Rather than the Exception

Fabio Moda[1], Arianna Ciullini[1], Ilaria Linda Dellarole[1], Annalisa Lombardo[1],
Nicole Campanella[1], Giuseppe Bufano[1], Federico Angelo Cazzaniga[1],
Giorgio Giaccone[1,*]

[1]Department of Neurology 5 - Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy
*Correspondence: giorgio.giaccone@istituto-besta.it (Giorgio Giaccone)
Academic Editor: Antoni Camins

Abstract

The presence of protein aggregates is a hallmark of many neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease (AD), and frontotemporal lobar degeneration (FTLD). Traditionally, each disease has been associated with the aggregation of specific proteins, which serve as disease-specific biomarkers. For example, aggregates of α-synuclein (α-syn) are found in α-synucleinopathies such as PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Similarly, AD is characterized by aggregates of amyloid-beta (Aβ) and tau proteins. However, it has been observed that these protein aggregates can also occur in other neurodegenerative diseases, contributing to disease progression. For instance, α-syn aggregates have been detected in AD, Down syndrome, Huntington's disease, prion diseases, and various forms of FTLD. Similarly, Aβ aggregates have been found in conditions like DLB and PD. Tau aggregates, in addition to being present in primary tauopathies, have been identified in prion diseases, α-synucleinopathies, and cognitively healthy aged subjects. Finally, aggregates of TDP-43, typically associated with FTLD and amyotrophic lateral sclerosis (ALS), have been observed in AD, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), MSA, DLB, and other neurodegenerative diseases. These findings highlight the complexity of protein aggregation in neurodegeneration and suggest potential interactions and common mechanisms underlying different diseases. A deeper understating of this complex scenario may eventually lead to the identification of a better elucidation of the pathogenetic mechanisms of these devastating conditions and hopefully new therapeutic stragegies.

Keywords: neurodegeneration; protein aggregation; biomarker; neuropathology; tautopathies; alpha-synucleinopathies; TDP-43 proteinopathies

1. Introduction: Brain Protein Aggregates - A Traditional View

Protein aggregation is a common feature of many neurodegenerative diseases (NDs), including Parkinson's disease (PD) and Alzheimer's disease (AD). According to traditional view, each ND is characterized by aggregation of one or two specific proteins, which are therefore considered disease-specific biomarkers and their detection and characteristic distribution pattern in the brain allow for a definitive disease diagnosis. Prior to aggregating, these proteins undergo conformational rearrangements which give them a propensity to clump and form toxic species that can impair brain functions. For instance, aggregates of aberrant α-synuclein (α-syn) are found in a group of pathologies referred to as α-synucleinopathies, which include, in addition to PD, also dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). The classification of these conditions depends on the clinical presentation and the spatiotemporal accumulation of pathological α-syn [1]. In PD, aggregates of α-syn are found within neurons of the substantia nigra and the basal forebrain but also in the cor-

tex, olfactory bulb and limbic system [2,3]. These species trigger the activation of glial cells and the release of pro-inflammatory cytokines which can result in cell death [4]. In DLB, α-syn often deposits within neurons of the neocortex, limbic system, brainstem and amygdala [5] while in MSA α-syn preferentially aggregates in oligodendrocytes, forming the typical glial cytoplasmic inclusions (GCIs) [6]. The involvement of α-syn in multiple disorders (PD, DLB and MSA) has allowed for the demonstration that this protein might exists as "strains", which are characterized by different aberrant structures and toxic properties, similarly to what has been widely described for prion diseases [7–13]. Different strains of α-syn are also believed to be responsible for the phenotypic heterogeneity of the same pathology, as in the case of PD [14,15] and MSA (that can present with parkinsonism (MSA-P) or cerebellar ataxia (MSA-C)) [16,17], although further studies are needed. Prion diseases are caused by the misfolding of the cellular prion protein (PrP^C) into a toxic species able to self-replicate named prion (PrP^{Sc}) which accumulates in the brain. PrP^{Sc} can adopt variable aberrant and toxic conformations that give rise to different diseases or disease-phenotypes, including

the sporadic Creutzfeldt-Jakob disease (sCJD) and the recently discovered variably protease-sensitive prionopathy (VPSPr) [13,18,19].

Aggregates of amyloid-beta (Aβ) and tau are the main hallmarks of AD: Aβ forms extracellular plaques whose deposition follows a spatiotemporal pathway beginning in the neocortex and then spreading to the allocortex, basal ganglia, midbrain, pons and cerebellum [20]; while tau forms intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated protein which spread from the transentorhinal region to the entorhinal region, hippocampus, temporal neocortex and superior temporal neocortex [20–22]. Aβ deposition precedes tau aggregation by several years or decades and preclinical studies have shown that Aβ is able to trigger the formation of NFTs, which more closely correlate with cognitive decline [23–25]. Interestingly, recent studies have suggested that the phenotypic heterogeneity of AD may be linked to the existence of various Aβ strains capable to affect distinct brain regions, as observed in the case of α-synucleinopathies [26–30]. Studies with ^{18}F-florbetapir positron emission tomography (PET) imaging performed on healthy subjects showed Aβ deposition in the cortex which increased with age and these findings were in accord with postmortem analyses, which showed an age-dependent increase of Aβ plaques in the brain of healthy individuals [31–33].

Aggregates of tau, TDP-43 or FUS (FUsed in Sarcoma protein) characterize a group of diseases known as frontotemporal lobar degeneration (FTLD) that can be classified in tauopathies, TDP-43 proteinopathies or FUS proteinopathies, respectively. Tauopathies (40% of FTLD cases) can be further divided in *primary tauopathies* which include corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), primary age-related tauopathy (PART), argyrophilic grain disease (AGD), tangle only dementia (TOD) and Pick's disease (PiD) [34]; or *secondary tauopathies,* where tau is not the unique pathological feature, and include AD and chronic traumatic encephalopathy (CTE) [35]. Primary and secondary tauopathies are characterized by the accumulation of abnormal tau protein in the form of neuropil threads, neurofibrillary tangles (NFTs) or tau-positive astrocytes [36–42]. The tau protein is usually associated to microtubules in neuronal cells and regulates their maintenance and shape as well as the axonal transport. Tau can be found also in astrocytes and oligodendrocytes. Once this protein undergoes aberrant conformational rearrangements, it aggregates most of the time under hyper-phosphorylated forms. Interestingly, the biochemical composition of tau which aggregates differ between diseases. For instance, PiD is characterized by the presence of tau isoform containing three microtubule-binding repeats (3R); while CBD, PSP and AGD show the presence of tau with four microtubule-binding repeats (4R). In the case of AD, the aggregates of tau are composed by both 3R and 4R isoforms [43–45].

As previously mentioned for α-syn and Aβ, the pathogenesis of tauopathies may involve the formation of distinct tau strains which can create unique patterns of neuropathology for each disease [46]. TDP-43 proteinopathies (45% of FTLD cases), include FTLD-TDP as well as amyotrophic lateral sclerosis (ALS) and limbic-predominant age-related TDP-43 encephalopathy (LATE) which are instead characterized by the presence of neuronal intranuclear and cytoplasmic inclusions of TDP-43, which is often hyper-phosphorylated, N-terminally truncated and ubiquitinated [47–54]. Interestingly, mutations in progranulin protein (PGRN) cause FTD with TDP-43 pathology [55]. Aggregates of toxic C-terminal TDP-43 species are found in the cytoplasm of neurons (in brain and spinal cord) of more than 97% of amyotrophic lateral sclerosis (ALS) cases and seems to impair neuronal proteostasis while promoting progressive loss of motor function [56–60]. The 90% of ALS are sporadic while approximately the 10% are caused by mutations in superoxide dismutase 1 (SOD1), C9orf72, fused in sarcoma (FUS) genes, or TAR DNA binding protein (TARDBP) [61]. In particular, there are several mutations affecting the TARDBP protein in different regions: N-terminal domain (e.g., D89E), RNA recognition motifs (e.g., K145Q, D219E) and C-terminal region (e.g., Q331K, M337V, Q343R, N345K, R361S, and N390D) [62].

Finally, FUS proteinopathies are the least common subtype of FTLD (5% of FTLD cases) and are characterized by the accumulation of FUS in neuronal cells [61,63,64]. The exact mechanisms through which Aβ, tau, α-syn, TDP-43 undergo misfolding and acquire disease-specific structures are now being elucidated. In addition to genetic proclivity to accumulate misfolded proteins, exposure to environmental toxins is now known to result in amino acid misincorporation and subsequent protein misfolding [65–67]. Certainly, these proteins are key players for the onset and progression of NDs and their detection as aggregated species in the brain is crucial for an accurate disease diagnosis. Through a prion-like mechanism, Aβ, tau, α-syn, TDP-43 spread from cell to cell in the brain thus allowing the propagation of pathology [68]. However, numerous studies have shown that some individuals show co-occurrence of more than one ND. In particular, aggregates composed of proteins which are not primarily involved in the pathological process of each ND can be found in postmortem brains (Fig. 1). These are considered secondary protein aggregates and may influence the clinical and neuropathological features of the NDs, although their role remain unknown. This work provides an up-to-date review of the literature on the presence of secondary aggregates in NDs.

2. Alpha-Synuclein Aggregates in Non-α-Synucleinopathies

Aggregates of misfolded α-syn are commonly found in the brains of patients with α-synucleinopathies, such as PD, DLB and MSA [69]. However, several works con-
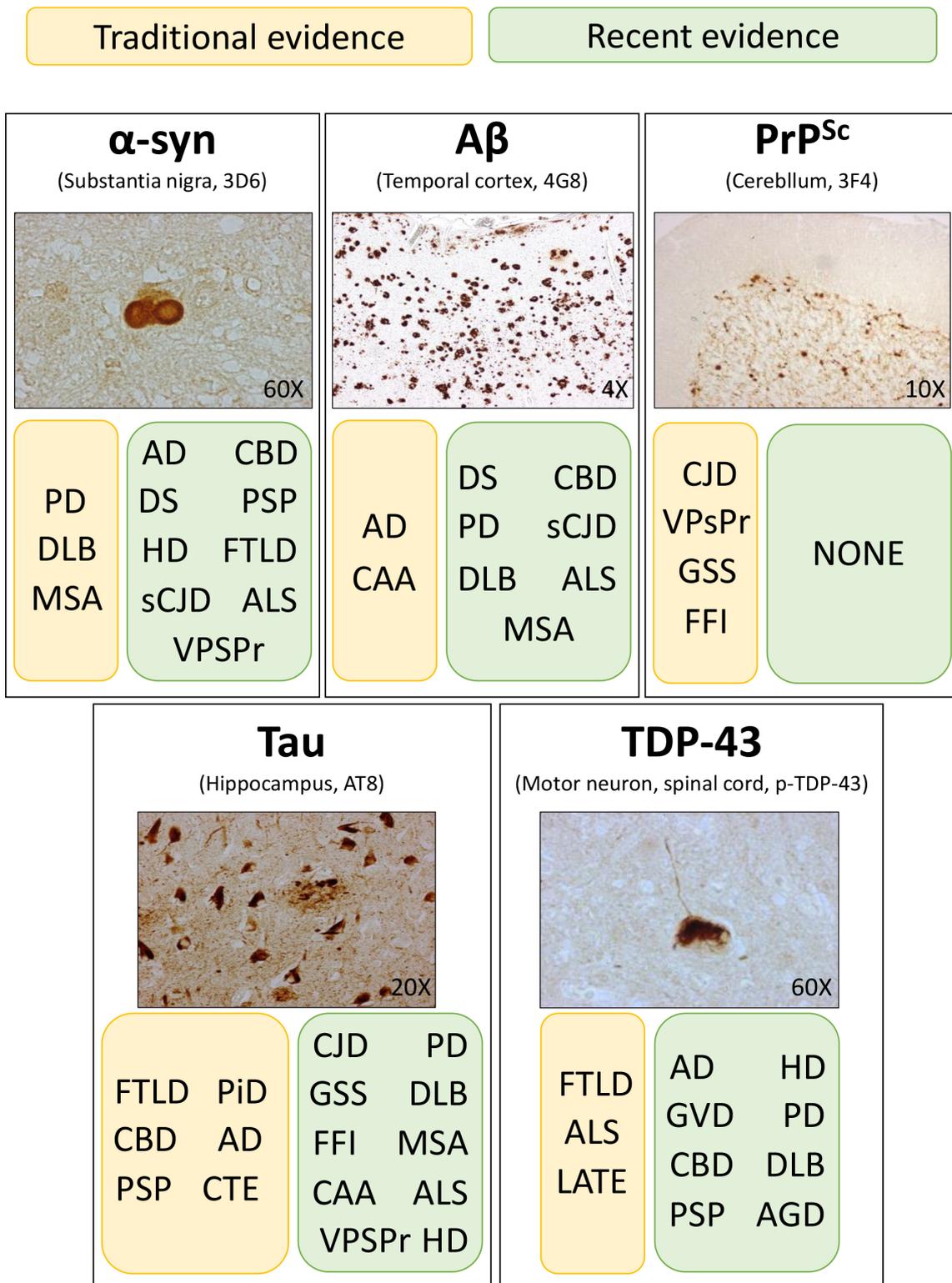
Fig. 1. Schematic representation of the traditional (yellow boxes) and recent (green boxes) evidence regarding protein aggregates in the central nervous system of patients with various neurodegenerative diseases. Histological stains show the typical morphological features of α-synuclein (α-syn), amyloid-β (Aβ), prion (PrP^{Sc}), tau and TDP-43 aggregates found in the brain of patients with PD, AD, CJD, AD and ALS, respectively. PD, Parkinson's disease; AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; ALS, amyotrophic lateral sclerosis.

firmed their presence, as secondary aggregates, in the brains of patients with other neurodegenerative diseases, including AD, Down syndrome (DS), Huntington's disease (HD), prion diseases, primary tauopathies (CBD and PSP), ALS, FTLD, parkinsonism-dementia complex of Guam [70–72] and neurodegeneration with brain iron accumulation type 1 [73,74]. The frequency of α-syn in most of these NDs is high and is considered the rule rather than the exception. Regarding AD, α-syn deposits were found in almost 50% of postmortem brains [75–77]. These aggregates were distributed in the neocortex, limbic system (being the amydgala highly vulnerable to α-syn pathology [78]) and substantia nigra of patients with sporadic and familial (*PSEN1*, *PSEN2* or *APP* gene mutations) forms of the disease [75,76,79–84]; often colocalizing with tau [75,77, 80,82] and less frequently with Aβ aggregates [81,83,85]. Therefore, α-syn pathology often accompanies AD pathology and, most importantly, it occurs in the brain of patients with specific clinical symptoms, including hallucinations, unexplained falls and extrapyramidal signs, constituting the nosologic entity of dementia with Lewy bodies (DLB) [5,21,75–77,79,80,82,86–90]. Remarkably, the presence or absence of α-syn aggregates in AD may further contribute to the phenotypic heterogeneity of the disease, making its clinical diagnosis even more challenging. In the case of DS, α-syn aggregates were identified mainly in the amygdala of more than 50% patients with behavioral decline and concomitant AD pathology and were absent in DS patients who lacked AD pathology or with preserved cognitive functions [91–93]. Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative condition characterized by the presence of an abnormal form of huntingtin (mHTT) protein which forms toxic intraneuronal inclusions, leading to choreatic movements, behavioral disturbances and dementia [94]. Aggregates of α-syn colocalized with mHTT inclusion of HD patients, although both proteins formed independent homomeric filaments. Thus, mHTT and α-syn and can cross-talk, with the latter being recruited as a mediator of toxicity in HD. In particular, α-syn may promote oxidative stress, mitochondrial disfunctions and brain inflammation [95–101], which are all implicated in disease pathogenesis [95,96,102–104]. In the case of prion diseases, α-syn aggregates were found with low prevalence (9–23%) in the brains of patients with sCJD and VPSPr [105]. The aggregates were observed in different brain areas, including the substantia nigra, locus coeruleus, dorsal motor nucleus of the vagus and cortical neurons [106], brainstem and amygdala [107] or even in glial cells of the striato-nigral-system [108]. They often co-deposited with other amyloidogenic proteins, including prion, Aβ and tau [105,109–113]. Notably, the presence of copathology was associated with a prolonged survival in patients with CJD [114]. Recent studies, performed under extreme and artificial conditions, showed that aggregates of α-syn can even cross-seed the aggregation of the prion pro-

tein, leading to the onset of prion diseases [115]. In the case of tauopathies, few studies reported the presence of α-syn aggregates in (1) CBD brains (sometimes in patients who had longer survival) [116–119], (2) PSP brains ($\sim$10–12% and mainly distributed in substantia nigra, basal forebrain, amygdala and frontal cortex) [120–124] and (3) a subgroup of sporadic or genetic FTD brains, especially in cases with concomitant motor neuron disease (FTD/ALS) [125–127]. α-syn aggregates were found to colocalize with SOD1 in familial ALS and it was shown that α-syn could accelerate SOD1 aggregation [128]. Moreover, α-syn aggregates deposited in astrocytes and Schwann cells in the spinal cords and bulbar regions, with a morphology resembling that of Lewy bodies found in PD [129]. The presence of α-syn aggregates in ALS supports their contribution to motor neuron disease pathology, as also observed in animal models. This also rules out PD as incidental pathology [129–137]. Remarkably, α-syn aggregates were described in 11–15% of ALS cases with TDP-43 pathology [138,139] and several works have shown that α-syn can directly interact with tau [140–143] and TDP-43 [144,145]. In particular, emerging evidence from preclinical models showed that α-syn and TDP-43 can form hybrid fibrils whose toxic properties are more severe compared to those of homotypic fibrils of α-syn or TDP-43 [145].

Finally, aggregates of α-syn were detected in the brain of cognitively healthy elderly subjects ($\sim$9–10%) [120,146] and these findings have allowed for the formulation of some hypotheses about their meaning: (1) they are inert species, (2) they represent common findings in normal ageing or (3) they represent an asymptomatic pathology in subjects at early disease stage [146–148]. The presence of α-syn aggregates in the brains of non-α-synucleinopathies has the potential to provide new insights into the complex neuropathology underlying NDs.

3. Amyloid-Beta Aggregates in Non AD Conditions

Aβ primarily occur in the brain of AD patients, but they can also occur in some non-AD conditions. For instance, Aβ deposition is present in the brains of nearly 30% of cognitively normal older individuals, as well as in patients with mild cognitive impairment (MCI) and dementia. In particular, neuropathological studies involving a small cohort of elderly non-demented subjects showed the presence of numerous Aβ deposits in the temporal cortex and large and round deposits in most cortical areas, similar to what is observed in AD brains [149,150]. Even more interestingly, the neuropathological analysis of the brain of centenarians, revealed that the highest stages of Aβ pathology were found in the brains of high performing subjects [151,152]. Therefore, Aβ deposition may be a common feature of brain aging and may contribute to predict the cognitive decline in some non-AD individuals [153]. The most

IMR Press

conservative interpretation is, therefore, that these represent early stages of AD pathology not (yet) inducing cognitive impairment.

Aβ deposits were also found in the brain of individuals with DS who have an increased expression of the amyloid precursor protein (APP) gene located on chromosome 21. Trisomy 21 leads to a dose-dependent increase in APP and Aβ production [154,155]. As a result, individuals with DS develop Aβ deposits in their brains at young age, and these deposits invariably lead to the development of AD later in life. In fact, the majority of DS individuals between the ages of 50 and 60 have an increased risk of developing dementia due to AD [156,157]. PET data analyses suggested that, similar to AD, Aβ deposits first occur in the striatum and gradually affect various cortical regions (affecting the rostral prefrontal and cingulate-parietal cortices) and finally the parahippocampal cortex, thalamus, and amygdala [158,159]. Aggregates of Aβ were found in the brains of some patients with DLB, suggesting that Aβ could contribute to the cognitive decline and alterations in attentive/executive and language functioning [160,161]. However, there is often an overlap between AD and DLB pathologies, thus other proteins (e.g., tau) may contribute to influence disease progression and dementia onset. Recent findings have suggested that there may also be some overlap between AD and PD. Specifically, some research has found evidence of Aβ plaques in the brains of individuals with Parkinson's disease, particularly in those who have cognitive impairment or dementia (PDD) in addition to their motor symptoms. In 2008, Kalaitzakis *et al*. [162], in a cohort of 30 patients (16 PDD, 14 PD), found that Aβ deposition was significantly more prevalent in the striatum (which includes the caudate nucleus, putamen, and nucleus accumbens) in PDD cases than in PD cases. One year later, the same research group described that Aβ deposition in the claustrum was associated with the occurrence of dementia in PD and DLB patients. The physiological role of the claustrum is mainly unknown, but it has been linked to the presence of visual hallucinations in DLB and cognitive impairment in AD [163]. Current evidence as postmortem, biochemical, and imaging analyses, increasingly indicate the involvement of Aβ in PD, and recent studies indicate a possible role of Aβ in gait disturbances and cognitive impairment in PD patients [164]. However, the role of Aβ in cognitive decline in PD requires further investigations [165,166]. Similarly, deposits of Aβ were described in the brain of a patient with MSA-C and in some cases of CBD and sCJD [167–173]. Even more intriguingly, altered level of APP, the Aβ precursor, was found in the brain, cerebrospinal fluid (CSF) and skin of patients with ALS and is considered an early indicator of neuromuscular junction instability and denervation [174]. *In vitro* studies have shown that Aβ interacts with SOD1 (an enzyme linked to ALS) and this lead to an impaired SOD1 enzymatic activity. Thus, Aβ may modulate ALS progression [175]. Another condition characterized by the presence of Aβ is the cerebral amyloid angiopathy (CAA), a cerebrovascular disease commonly observed among the elderly [176]. In this case, the deposition of Aβ occurs mainly within cortical and leptomeningeal arteries, capillaries and arterioles and may cause spontaneous intracerebral hemorrhages (ICHs), other neurologic symptoms or may remain asymptomatic [177]. While CAA is characterized by amyloid deposition in vasculature with posterior microbleeds and vascular cognitive impairment, AD involves amyloid deposition in brain parenchyma and also leads to cognitive impairment. CAA is recognized as a leading cause of subarachnoid hemorrhage [178] and the co-occurrence of CAA and AD pathology is often observed in the same brain, with a higher incidence in symptomatic AD patients. However, no significant correlation was found between the severity of AD and CAA pathology [179,180]. Interestingly, CAA can be observed in cognitively normal subjects who test positive for Aβ on PET imaging [181]. This suggests that CAA may occur independently of AD [180,182].

4. Tau Aggregates in the Brain of Non-Primary Tauopathies

Aggregates of misfolded tau are commonly found in the brains of patients with primary and secondary tauopathies, including AD, CTE, CBD, PSP AGD, TOD, PART and PiD. However, tau aggregates can be found also in other neurodegenerative diseases. For instance, tau aggregates could be observed in the brain of patients with prion diseases, including cases of PrP cerebral amyloid angiopathy, Gerstmann-Sträussler-Scheinker (GSS), fatal familial insomnia (FFI), variant Creutzfeldt-Jakob disease (vCJD) and VPSPr [183–185]. In sCJD the frequency of tau deposition is not unusually high but it does not often relate to prion deposition [186]. However, in GSS tau deposition was found to parallel PrP aggregation, with a cortical distribution that can reach the deepest neuronal layers. This specific pattern of tau deposition is mainly observed in GSS cases with a stop-mutation in the PRNP gene at codons 145, 198 and 217 which are therefore characterized by a higher degree of neuronal degeneration [187]. Tau deposits were found in the brain of patients with α-synucleinopathies. In particular, tau aggregates were found in dopaminergic neurons of the nigrostriatal region in patients with PD, and PD with dementia; while in the case of DLB, tau and α-synuclein have been found to codeposit in the same neuronal populations [188,189]. Interestingly, in DLB, there is a frequent overlap among α-synuclein, tau, and β-amyloid pathologies which supports the combined contribution of each protein in disease onset and progression [190]. A few reports have shown the presence of tau aggregates in the brain of patients with MSA with longer disease duration. In these cases, tau and α-synuclein were found to co-occur in neuronal and glial cytoplasmic inclusions (NCIs and GCIs, respectively) [191]. *In vitro* studies have shown that, in

some cases, tau enhances α-synuclein toxicity [192,193]. Tau aggregates were also observed in the astrocytes of a subgroup of ALS cases with cognitive impairment [194]. However, tau aggregation often occurs in Western Pacific variant of ALS in which ALS, parkinsonism, and dementia co-occur. In this variant, tau-immunoreactive neuronal inclusions with the morphology of neurofibrillary tangles (NFTs) are found in the II and III layers of the frontal cortex [195]. Remarkably, tau pathology is present in many cases of CAA [196]. These findings provide evidence for a cohesive pathological mechanism in which the accumulation of amyloidogenic peptides within the vasculature initiates a complex sequence of pathological events, ultimately resulting in the aggregation of tau and subsequent neurodegeneration [197]. Tau aggregates are also found in the brain of patients with HD and mouse models of the disease [198,199]. Remarkably, unique expression patterns of tau isoforms were described in the cortex and putamen of individuals affected by HD [200]. Interestingly, the presence of an attenuated motor phenotype of HTT transgenic mice with genetic tau reduction indicates a role of tau in HD pathogenesis [201].

Even with the physiological aging, there is a normal phosphorylated-tau deposition in the brain [202]. The PART, describes a group of conditions commonly observed in the brains of aged subjects that are characterized by the presence of neurofibrillary tangles (NFT) that are indistinguishable from those of AD, in the absence of Aβ plaques [39]. PART represents a pathologic continuum which spans from a condition of focal distribution of neurofibrillary tangles (NFT) in cognitively normal aged individuals, to pathological situations that include the tangle-predominant senile dementia (TPSD), the TOD, the preferential development of NFT without senile plaques, and the senile dementia of the neurofibrillary tangle type (SD-NFT) [39].

5. TDP-43 Aggregates in Non TDP-43 Proteinopathies

TDP-43 is mainly localized in the nucleus and is involved in RNA regulation, including transcription, splicing and stabilization [203,204]. The protein can undergo several post-translational modifications (e.g., hyperphosphorylation, cleavage, ubiquitination) which lead to its cytoplasmic aggregation [62,205]. TDP-43 inclusion bodies are commonly observed in neurons and glial cells of patients with ALS, FTLD-TDP and LATE [62,206]. However, several studies showed that aggregates of TDP-43 occurs in the brain of patients with other neurodegenerative diseases as well as neurologically normal subjects. For instance, TDP-43 pathology is present in up to 57% of AD cases [207,208]. Interestingly, TDP-43 species were found to colocalize with Aβ and tau aggregates and were responsible for a more severe AD pathology, including greater brain atrophy and memory loss [209]. TDP-43 deposition was common in limbic predominant and typical AD subtypes

(67% and 59%, respectively), but less prevalent in the hippocampal sparing subtype (21%) [210]. This suggests that TDP-43 can either influence AD progression and clinical features (representing a risk factor for developing dementia) or be the results of neuropathological changes occurring in advanced AD. Regardless of the AD subtypes, the presence of TDP-43 aggregates always correlate with worse clinical progression. The deposition of TDP-43 follows a specific staging scheme which involves: amygdala (stage 1); enthorhinal cortex and subiculum of the hippocampus (stage 2); dentate gyrus of the hippocampus and occipitotemporal cortex (stage 3); insular cortex, basal forebrain, inferior temporal cortex and ventral striatum (stage 4); brainstem nuclei (stage 5) and basal ganglia and middle frontal cortex (stage 6) [211]. *In vitro* and *in vivo* studies have shown that oligomers of Aβ or tau are able to cross-seed the polymerization of TDP-43 into pathological aggregates [212] and TDP-43 may regulate Aβ clearance [208,213]. Granulovacuolar degeneration (GVD) may occur as AD copathology and is characterized by the accumulation of TDP-43 along with other proteins associated with AD [214].

In the case of PSP, a study published in 2016 showed that out of 945 cases of pathologically confirmed cases, 56 ($\sim$7%) of them were found to have TDP-43 aggregates mainly affecting the amygdala or hippocampus, or both. Interestingly, the progression pattern of TDP-43 aggregates was very similar to that observed in AD, more than that typically observed in ALS or FTLD-TDP [215]. A more recent study showed that 10 out of 26 spinal cord samples of PSP patients contained aggregates of TDP-43 (38%), mainly in motor neurons [216]. The aggregates were composed of the insoluble C-terminal part of TDP-43.

Compared to PSP, CBD patients are more vulnerable to TDP-43 pathology. In particular, in a study published in 2018, of the 187 CBD cases the 45% showed TDP-43 aggregates, often involving brainstem, pons, subthalamic nucleus, posterior hypothalamus, superior frontal gyrus and cingulate gyrus [217]. A more recent study confirmed the presence of TDP-43 aggregates in spinal cord samples of CBD patients [216]. In contrast, previous studies reported lower coincidental deposition of TDP-43 in CBD cases, spanning from 9% to 24%, but this discrepancy was associated with differences in the screening methods used [138,218,219]. Interestingly, the higher prevalence of TDP-43 pathology in CBD than PSP patients can help to distinguish these diseases, especially in patients presenting with PSP syndrome. Indeed, TDP-43 pathology significantly influences CBD clinical features. For instance, the presence of TDP-43 aggregates in the midbrain tectum of CBD patients may lead to a clinical PSP presentation. Unlike AD, the amygdala of CBD cases was less affected by TDP-43 aggregation, while the midbrain, subthalamic nucleus and pons were found to be the most vulnerable regions [217].

TDP-43 aggregates with oval, round and ellipsoid shapes were found to colocalize with hungtingtin (HTT) inclusions in cortex and basal ganglia of HD cases [220,221]. Both TDP-43 and HTT proteins are involved in transcriptional regulation and similar to TDP-43 [222], HTT inclusions occur in cytoplasm and nucleus [220].

TDP-43 copathology has been reported also in the brain of patients with MSA, PD and DLB. In particular, TDP-43 aggregates occur infrequently in MSA ($\sim$7% of the cases analyzed) and mainly localize in the medial temporal lobe of aged patients. TDP-43 aggregates were found also to colocalize with α-synuclein in GCIs indicating a possible interation between the two proteins [223]. Similarly, TDP-43 inclusions were reported in the 7% of PD cases and in the 19% of PD cases with dementia [224]. Conversely, in the context of DLB, TDP-43 inclusions are observed with divergent prevalence spanning from 0% to 56% [224–227] and their distribution mainly affect the amygdala and hippocampal structures, as observed in AD. Interestingly, cingulate and insular cortices were not involved, unlike AD [228]. *In vitro* studies have shown that the co-occurrence of TDP-43 and α-synuclein lead to a more severe α-synuclein pathology [229,230], likely because TDP-43 is able to enhance the toxicity of α-synuclein [231].

Aggregates of TDP-43 were also observed in the brain of patients with AGD, especially in cases with severe grain pathology. This study suggests that abnormal accumulation of TDP-43 may be involved in AGD pathological process and disease progression. However these findings are still controversial since other studies postulated that TDP-43 pathology does not significantly impact the clinical presentation of AGD [232]. Interestingly, in most AGD cases, TDP-43 pathology was consistent with LATE [233].

Finally, TDP-43 aggregates were found in the brain of aged cognitively normal individuals with an incidence ranging between 11% and 36% and increasing with age [225,234,235], suggesting that this phenomenon may be age-dependent but its interpretation is still controversial.

6. Discussion

The concept of identifying a specific neurodegenerative disease based on the accumulation of a particular protein in the brain (such as tau, TDP43, α-syn) is appealing and has been crucial for molecular classification. However, this idea is becoming increasingly challenged by the fact that, more often than not, multiple proteins aggregate in a single brain, leading to copathologies that stratify upon the original disease [236]. In some cases, it may even be unclear which condition was the original one.

We have presented a detailed list of protein aggregates that have been reported to associate with the main proteinopathy in different neurodegenerative diseases. It is therefore clear that the occurrence of copathologies represents almost the rule rather than the exceptions in this field.

This may represent the molecular basis of the extreme phenotypic variability that has been extensively described for example in Alzheimer disease. AD may coexist with α-synuclein pathology in DLB, with TDP-43 pathology in LATE. The coexistence of AD pathology and PART may be postulated and would be impossible to resolve as tau pathology of AD and PART are not distinguishable.

Our knowledge on this field is limited by the difficulties of performing large-scale post mortem neuropathological studies that are the only way to obtain detailed description of protein-aggregates topography and burden.

7. Conclusions

This review highlights the complexity of protein aggregation in neurodegeneration and suggests potential common mechanisms and interactions underlying different diseases. The traditional view of each neurodegenerative disease (ND) being exclusively associated with a single protein aggregate is being challenged, and the coexistence of multiple proteinopathies may contribute to the phenotypic heterogeneity observed in these conditions. In this scenario, achieving a precise understanding of the pathological processes occurring during a ND in a living patient can be accomplished through specific biomarkers tailored to each proteinopathy. Over the past few years, numerous methods have been developed to analyze promising peripheral biomarkers, such as seed amplification assays, which have the potential to enhance the clinical diagnosis of neurodegenerative diseases (NDs). However, considering the complexity of NDs, it is likely that multiple approaches would be necessary to identify novel and reliable biomarkers for a paradigm shift towards a more precise biological-based diagnosis which overcomes the limits of clinical interpretation. Further research in this field will likely lead to more comprehensive and accurate disease classifications and therapeutic approaches aimed at targeting the shared pathological mechanisms across multiple neurodegenerative disorders. Ultimately, the hope is that these efforts will pave the way for improved treatments and better outcomes for patients affected by these devastating diseases.

Funding

Conflict of Interest

References

[1] Kovacs GG. Molecular Pathological Classification of Neurodegenerative Diseases: Turning towards Precision Medicine. International Journal of Molecular Sciences. 2016; 17: 189.

[2] Forno LS. Neuropathology of Parkinson's disease. Journal of Neuropathology and Experimental Neurology. 1996; 55: 259–272.

[3] Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Movement Disorders: Official Journal of the Movement Disorder Society. 2012; 27: 8–30.

[4] Tufi R, Gandhi S, de Castro IP, Lehmann S, Angelova PR, Dinsdale D, et al. Enhancing nucleotide metabolism protects against mitochondrial dysfunction and neurodegeneration in a PINK1 model of Parkinson's disease. Nature Cell Biology. 2014; 16: 157–166.

[5] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017; 89: 88–100.

[6] Peng C, Gathagan RJ, Covell DJ, Medellin C, Stieber A, Robinson JL, et al. Cellular milieu imparts distinct pathological α-synuclein strains in α-synucleinopathies. Nature. 2018; 557: 558–563.

[7] Malfertheiner K, Stefanova N, Heras-Garvin A. The Concept of α-Synuclein Strains and How Different Conformations May Explain Distinct Neurodegenerative Disorders. Frontiers in Neurology. 2021; 12: 737195.

[8] Lau A, So RWL, Lau HHC, Sang JC, Ruiz-Riquelme A, Fleck SC, et al. α-Synuclein strains target distinct brain regions and cell types. Nature Neuroscience. 2020; 23: 21–31.

[9] Hoppe SO, Uzunoğlu G, Nussbaum-Krammer C. α-Synuclein Strains: Does Amyloid Conformation Explain the Heterogeneity of Synucleinopathies? Biomolecules. 2021; 11: 931.

[10] Bousset L, Pieri L, Ruiz-Arlandis G, Gath J, Jensen PH, Habenstein B, et al. Structural and functional characterization of two alpha-synuclein strains. Nature Communications. 2013; 4: 2575.

[11] Yang Y, Shi Y, Schweighauser M, Zhang X, Kotecha A, Murzin AG, et al. Structures of α-synuclein filaments from human brains with Lewy pathology. Nature. 2022; 610: 791–795.

[12] Morales R, Abid K, Soto C. The prion strain phenomenon: molecular basis and unprecedented features. Biochimica et Biophysica Acta. 2007; 1772: 681–691.

[13] Morales R. Prion strains in mammals: Different conformations leading to disease. PLoS Pathogens. 2017; 13: e1006323.

[14] Foltynie T, Brayne C, Barker RA. The heterogeneity of idiopathic Parkinson's disease. Journal of Neurology. 2002; 249: 138–145.

[15] Angeli A, Mencacci NE, Duran R, Aviles-Olmos I, Kefalopoulou Z, Candelario J, et al. Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation. Movement Disorders: Official Journal of the Movement Disorder Society. 2013; 28: 1370–1375.

[16] Jellinger KA. Heterogeneity of Multiple System Atrophy: An Update. Biomedicines. 2022; 10: 599.

[17] Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008; 71: 670–676.

[18] Gambetti P, Puoti G, Zou WQ. Variably protease-sensitive prionopathy: a novel disease of the prion protein. Journal of Molecular Neuroscience: MN. 2011; 45: 422–424.

[19] Safar J, Wille H, Itri V, Groth D, Serban H, Torchia M, et al. Eight prion strains have PrP(Sc) molecules with different conformations. Nature Medicine. 1998; 4: 1157–1165.

[20] Thal DR, Attems J, Ewers M. Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies. Journal of Alzheimer's Disease: JAD. 2014; 42: S421–S429.

[21] Twohig D, Nielsen HM. α-synuclein in the pathophysiology of Alzheimer's disease. Molecular Neurodegeneration. 2019; 14: 23.

[22] Selkoe DJ. Alzheimer's disease is a synaptic failure. Science (New York, N.Y.). 2002; 298: 789–791.

[23] Hansson O. Biomarkers for neurodegenerative diseases. Nature Medicine. 2021; 27: 954–963.

[24] Doré V, Krishnadas N, Bourgeat P, Huang K, Li S, Burnham S, et al. Relationship between amyloid and tau levels and its impact on tau spreading. European Journal of Nuclear Medicine and Molecular Imaging. 2021; 48: 2225–2232.

[25] Pichet Binette A, Franzmeier N, Spotorno N, Ewers M, Brendel M, Biel D, et al. Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. Nature Communications. 2022; 13: 6635.

[26] Rasmussen J, Mahler J, Beschorner N, Kaeser SA, Häsler LM, Baumann F, et al. Amyloid polymorphisms constitute distinct clouds of conformational variants in different etiological subtypes of Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2017; 114: 13018–13023.

[27] Condello C, Lemmin T, Stöhr J, Nick M, Wu Y, Maxwell AM, et al. Structural heterogeneity and intersubject variability of Aβ in familial and sporadic Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2018; 115: E782–E791.

[28] Condello C, Stöehr J. Aβ propagation and strains: Implications for the phenotypic diversity in Alzheimer's disease. Neurobiology of Disease. 2018; 109: 191–200.

[29] Di Fede G, Catania M, Maderna E, Ghidoni R, Benussi L, Tonoli E, et al. Molecular subtypes of Alzheimer's disease. Scientific Reports. 2018; 8: 3269.

[30] Cohen M, Appleby B, Safar JG. Distinct prion-like strains of amyloid beta implicated in phenotypic diversity of Alzheimer's disease. Prion. 2016; 10: 9–17.

[31] Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiology of Aging. 1997; 18: 351–357.

[32] Price JL, McKeel DW, Jr, Buckles VD, Roe CM, Xiong C, Grundman M, et al. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. Neurobiology of Aging. 2009; 30: 1026–1036.

[33] Rodrigue KM, Kennedy KM, Devous MD, Sr, Rieck JR, Hebrank AC, Diaz-Arrastia R, et al. β-Amyloid burden in healthy aging: regional distribution and cognitive consequences. Neurology. 2012; 78: 387–395.

[34] Spillantini MG, Goedert M. Tau pathology and neurodegeneration. The Lancet. Neurology. 2013; 12: 609–622.

[35] Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, et al. Clinicopathological Evaluation

of Chronic Traumatic Encephalopathy in Players of American Football. JAMA. 2017; 318: 360–370.

[36] Silva MC, Haggarty SJ. Tauopathies: Deciphering Disease Mechanisms to Develop Effective Therapies. International Journal of Molecular Sciences. 2020; 21: 8948.

[37] Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annual Review of Neuroscience. 2001; 24: 1121–1159.

[38] Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. Acta Neuropathologica. 2011; 122: 137–153.

[39] Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathologica. 2014; 128: 755–766.

[40] Irwin DJ, Brettschneider J, McMillan CT, Cooper F, Olm C, Arnold SE, et al. Deep clinical and neuropathological phenotyping of Pick disease. Annals of Neurology. 2016; 79: 272–287.

[41] Rankin KP, Mayo MC, Seeley WW, Lee S, Rabinovici G, Gorno-Tempini ML, et al. Behavioral variant frontotemporal dementia with corticobasal degeneration pathology: phenotypic comparison to bvFTD with Pick's disease. Journal of Molecular Neuroscience: MN. 2011; 45: 594–608.

[42] Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013; 80: 496–503.

[43] Yoshida M. Cellular tau pathology and immunohistochemical study of tau isoforms in sporadic tauopathies. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2006; 26: 457–470.

[44] Kolarova M, García-Sierra F, Bartos A, Ricny J, Ripova D. Structure and pathology of tau protein in Alzheimer disease. International Journal of Alzheimer's Disease. 2012; 2012: 731526.

[45] Hardy J. Testing times for the "amyloid cascade hypothesis". Neurobiology of Aging. 2002; 23: 1073–1074.

[46] Vaquer-Alicea J, Diamond MI, Joachimiak LA. Tau strains shape disease. Acta Neuropathologica. 2021; 142: 57–71.

[47] Dugger BN, Dickson DW. Pathology of Neurodegenerative Diseases. Cold Spring Harbor Perspectives in Biology. 2017; 9: a028035.

[48] Mackenzie IRA, Bigio EH, Ince PG, Geser F, Neumann M, Cairns NJ, et al. Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. Annals of Neurology. 2007; 61: 427–434.

[49] Neumann M, Kwong LK, Truax AC, Vanmassenhove B, Kretzschmar HA, Van Deerlin VM, et al. TDP-43-positive white matter pathology in frontotemporal lobar degeneration with ubiquitin-positive inclusions. Journal of Neuropathology and Experimental Neurology. 2007; 66: 177–183.

[50] Hasegawa M, Arai T, Nonaka T, Kametani F, Yoshida M, Hashizume Y, et al. Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Annals of Neurology. 2008; 64: 60–70.

[51] Igaz LM, Kwong LK, Xu Y, Truax AC, Uryu K, Neumann M, et al. Enrichment of C-terminal fragments in TAR DNA-binding protein-43 cytoplasmic inclusions in brain but not in spinal cord of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. The American Journal of Pathology. 2008; 173: 182–194.

[52] Prasad A, Bharathi V, Sivalingam V, Girdhar A, Patel BK. Molecular Mechanisms of TDP-43 Misfolding and Pathology in Amyotrophic Lateral Sclerosis. Frontiers in Molecular Neuroscience. 2019; 12: 25.

[53] Neumann M, Kwong LK, Lee EB, Kremmer E, Flatley A, Xu Y, et al. Phosphorylation of S409/410 of TDP-43 is a consistent feature in all sporadic and familial forms of TDP-43 proteinopathies. Acta Neuropathologica. 2009; 117: 137–149.

[54] Neumann M, Mackenzie IR, Cairns NJ, Boyer PJ, Markesbery WR, Smith CD, et al. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. Journal of Neuropathology and Experimental Neurology. 2007; 66: 152–157.

[55] Beel S, Herdewyn S, Fazal R, De Decker M, Moisse M, Robberecht W, et al. Progranulin reduces insoluble TDP-43 levels, slows down axonal degeneration and prolongs survival in mutant TDP-43 mice. Molecular Neurodegeneration. 2018; 13: 55.

[56] Ling SC, Polymenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. Neuron. 2013; 79: 416–438.

[57] Tan RH, Ke YD, Ittner LM, Halliday GM. ALS/FTLD: experimental models and reality. Acta Neuropathologica. 2017; 133: 177–196.

[58] Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science (New York, N.Y.). 2006; 314: 130–133.

[59] Vanden Broeck L, Kleinberger G, Chapuis J, Gistelinck M, Amouyel P, Van Broeckhoven C, et al. Functional complementation in Drosophila to predict the pathogenicity of TARDBP variants: evidence for a loss-of-function mechanism. Neurobiology of Aging. 2015; 36: 1121–1129.

[60] Ederle H, Dormann D. TDP-43 and FUS en route from the nucleus to the cytoplasm. FEBS Letters. 2017; 591: 1489–1507.

[61] Mathis S, Goizet C, Soulages A, Vallat JM, Masson GL. Genetics of amyotrophic lateral sclerosis: A review. Journal of the Neurological Sciences. 2019; 399: 217–226.

[62] Jo M, Lee S, Jeon YM, Kim S, Kwon Y, Kim HJ. The role of TDP-43 propagation in neurodegenerative diseases: integrating insights from clinical and experimental studies. Experimental & Molecular Medicine. 2020; 52: 1652–1662.

[63] Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathologica. 2010; 119: 1–4.

[64] Mackenzie IRA, Neumann M. Molecular neuropathology of frontotemporal dementia: insights into disease mechanisms from postmortem studies. Journal of Neurochemistry. 2016; 138: 54–70.

[65] Cox PA, Davis DA, Mash DC, Metcalf JS, Banack SA. Dietary exposure to an environmental toxin triggers neurofibrillary tangles and amyloid deposits in the brain. Proceedings. Biological Sciences. 2016; 283: 20152397.

[66] Davis DA, Cox PA, Banack SA, Lecusay PD, Garamszegi SP, Hagan MJ, et al. l-Serine Reduces Spinal Cord Pathology in a Vervet Model of Preclinical ALS/MND. Journal of Neuropathology and Experimental Neurology. 2020; 79: 393–406.

[67] Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, et al. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science (New York, N.Y.). 2012; 338: 949–953.

[68] Goedert M. NEURODEGENERATION. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. Science (New York, N.Y.). 2015; 349: 1255555.

[69] Goedert M, Jakes R, Spillantini MG. The Synucleinopathies: Twenty Years On. Journal of Parkinson's Disease. 2017; 7: S51–S69.

[70] Yamazaki M, Arai Y, Baba M, Iwatsubo T, Mori O, Katayama Y, et al. Alpha-synuclein inclusions in amygdala in the brains of patients with the parkinsonism-dementia complex of Guam. Journal of Neuropathology and Experimental Neurology. 2000;

59: 585–591.

[71] Goedert M. Alpha-synuclein and neurodegenerative diseases. Nature Reviews. Neuroscience. 2001; 2: 492–501.

[72] Forman MS, Schmidt ML, Kasturi S, Perl DP, Lee VMY, Trojanowski JQ. Tau and alpha-synuclein pathology in amygdala of Parkinsonism-dementia complex patients of Guam. The American Journal of Pathology. 2002; 160: 1725–1731.

[73] Neumann M, Adler S, Schlüter O, Kremmer E, Benecke R, Kretzschmar HA. Alpha-synuclein accumulation in a case of neurodegeneration with brain iron accumulation type 1 (NBIA-1, formerly Hallervorden-Spatz syndrome) with widespread cortical and brainstem-type Lewy bodies. Acta Neuropathologica. 2000; 100: 568–574.

[74] Galvin JE, Giasson B, Hurtig HI, Lee VM, Trojanowski JQ. Neurodegeneration with brain iron accumulation, type 1 is characterized by alpha-, beta-, and gamma-synuclein neuropathology. The American Journal of Pathology. 2000; 157: 361–368.

[75] Lippa CF, Fujiwara H, Mann DM, Giasson B, Baba M, Schmidt ML, et al. Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. The American Journal of Pathology. 1998; 153: 1365–1370.

[76] Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. Brain Pathology (Zurich, Switzerland). 2000; 10: 378–384.

[77] Arai Y, Yamazaki M, Mori O, Muramatsu H, Asano G, Katayama Y. Alpha-synuclein-positive structures in cases with sporadic Alzheimer's disease: morphology and its relationship to tau aggregation. Brain Research. 2001; 888: 287–296.

[78] Parkkinen L, Soininen H, Alafuzoff I. Regional distribution of alpha-synuclein pathology in unimpaired aging and Alzheimer disease. Journal of Neuropathology and Experimental Neurology. 2003; 62: 363–367.

[79] Hansen LA, Masliah E, Galasko D, Terry RD. Plaque-only Alzheimer disease is usually the lewy body variant, and vice versa. Journal of Neuropathology and Experimental Neurology. 1993; 52: 648–654.

[80] Marui W, Iseki E, Uéda K, Kosaka K. Occurrence of human alpha-synuclein immunoreactive neurons with neurofibrillary tangle formation in the limbic areas of patients with Alzheimer's disease. Journal of the Neurological Sciences. 2000; 174: 81–84.

[81] Wirths O, Weickert S, Majtenyi K, Havas L, Kahle PJ, Okochi M, et al. Lewy body variant of Alzheimer's disease: alpha-synuclein in dystrophic neurites of A beta plaques. Neuroreport. 2000; 11: 3737–3741.

[82] Iseki E. Dementia with Lewy bodies: reclassification of pathological subtypes and boundary with Parkinson's disease or Alzheimer's disease. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2004; 24: 72–78.

[83] Mikolaenko I, Pletnikova O, Kawas CH, O'Brien R, Resnick SM, Crain B, et al. Alpha-synuclein lesions in normal aging, Parkinson disease, and Alzheimer disease: evidence from the Baltimore Longitudinal Study of Aging (BLSA). Journal of Neuropathology and Experimental Neurology. 2005; 64: 156–162.

[84] Mukaetova-Ladinska EB, Hurt J, Jakes R, Xuereb J, Honer WG, Wischik CM. Alpha-synuclein inclusions in Alzheimer and Lewy body diseases. Journal of Neuropathology and Experimental Neurology. 2000; 59: 408–417.

[85] Tsigelny IF, Crews L, Desplats P, Shaked GM, Sharikov Y, Mizuno H, et al. Mechanisms of hybrid oligomer formation in the pathogenesis of combined Alzheimer's and Parkinson's diseases. PloS one. 2008; 3: e3135.

[86] Förstl H, Burns A, Luthert P, Cairns N, Levy R. The Lewy-body variant of Alzheimer's disease. Clinical and pathological findings. The British Journal of Psychiatry: the Journal of Mental

Science. 1993; 162: 385–392.

[87] Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, Katzman R, et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology. 1998; 51: 351–357.

[88] McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996; 47: 1113–1124.

[89] Cook C, Petrucelli L. Aβ Puts the Alpha in Synuclein. Neuron. 2020; 105: 205–206.

[90] Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, DeTeresa R, et al. The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. Neurology. 1990; 40: 1–8.

[91] Lippa CF, Schmidt ML, Lee VM, Trojanowski JQ. Antibodies to alpha-synuclein detect Lewy bodies in many Down's syndrome brains with Alzheimer's disease. Annals of Neurology. 1999; 45: 353–357.

[92] Bodhireddy S, Dickson DW, Mattiace L, Weidenheim KM. A case of Down's syndrome with diffuse Lewy body disease and Alzheimer's disease. Neurology. 1994; 44: 159–161.

[93] Raghavan R, Khin-Nu C, Brown A, Irving D, Ince PG, Day K, et al. Detection of Lewy bodies in Trisomy 21 (Down's syndrome). The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques. 1993; 20: 48–51.

[94] Roos RAC. Huntington's disease: a clinical review. Orphanet Journal of Rare Diseases. 2010; 5: 40.

[95] Tomás-Zapico C, Díez-Zaera M, Ferrer I, Gómez-Ramos P, Morán MA, Miras-Portugal MT, et al. α-Synuclein accumulates in huntingtin inclusions but forms independent filaments and its deficiency attenuates early phenotype in a mouse model of Huntington's disease. Human Molecular Genetics. 2012; 21: 495–510.

[96] Chánez-Cárdenas ME, Vázquez-Contreras E. The Aggregation of Huntingtin and α-Synuclein. Journal of Biophysics (Hindawi Publishing Corporation: Online). 2012; 2012: 606172.

[97] Corrochano S, Renna M, Carter S, Chrobot N, Kent R, Stewart M, et al. α-Synuclein levels modulate Huntington's disease in mice. Human Molecular Genetics. 2012; 21: 485–494.

[98] Poças GM, Branco-Santos J, Herrera F, Outeiro TF, Domingos PM. α-Synuclein modifies mutant huntingtin aggregation and neurotoxicity in Drosophila. Human Molecular Genetics. 2015; 24: 1898–1907.

[99] Breza M, Emmanouilidou E, Leandrou E, Kartanou C, Bougea A, Panas M, et al. Elevated Serum α-Synuclein Levels in Huntington's Disease Patients. Neuroscience. 2020; 431: 34–39.

[100] Herrera F, Outeiro TF. α-Synuclein modifies huntingtin aggregation in living cells. FEBS Letters. 2012; 586: 7–12.

[101] Yu D, Zarate N, White A, Coates D, Tsai W, Nanclares C, et al. CK2 alpha prime and alpha-synuclein pathogenic functional interaction mediates synaptic dysregulation in huntington's disease. Acta Neuropathologica Communications. 2022; 10: 83.

[102] Charles V, Mezey E, Reddy PH, Dehejia A, Young TA, Polymeropoulos MH, et al. Alpha-synuclein immunoreactivity of huntingtin polyglutamine aggregates in striatum and cortex of Huntington's disease patients and transgenic mouse models. Neuroscience Letters. 2000; 289: 29–32.

[103] Alves S, Régulier E, Nascimento-Ferreira I, Hassig R, Dufour N, Koeppen A, et al. Striatal and nigral pathology in a lentiviral rat model of Machado-Joseph disease. Human Molecular Genetics. 2008; 17: 2071–2083.

[104] Berciano J, Ferrer I. Glial cell cytoplasmic inclusions in SCA2 do not express alpha-synuclein. Journal of Neurology. 2005; 252: 742–744.

[105] Grau-Rivera O, Gelpi E, Nos C, Gaig C, Ferrer I, Saiz A, *et al.* Clinicopathological Correlations and Concomitant Pathologies in Rapidly Progressive Dementia: A Brain Bank Series. Neurodegenerative Diseases. 2015; 15: 350–360.

[106] Vital A, Canron MH, Gil R, Hauw JJ, Vital C. A sporadic case of Creutzfeldt-Jakob disease with beta-amyloid deposits and alpha-synuclein inclusions. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2007; 27: 273–277.

[107] Fernández-Vega I, Ruiz-Ojeda J, Juste RA, Geijo M, Zarranz JJ, Sánchez Menoyo JL, *et al.* Coexistence of mixed phenotype Creutzfeldt-Jakob disease, Lewy body disease and argyrophilic grain disease plus histological features of possible Alzheimer's disease: a multi-protein disorder in an autopsy case. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2015; 35: 56–63.

[108] Rodriguez-Diehl R, Rey MJ, Gironell A, Martinez-Saez E, Ferrer I, Sánchez-Valle R, *et al.* "Preclinical" MSA in definite Creutzfeldt-Jakob disease. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2012; 32: 158–163.

[109] Vital A, Fernagut PO, Canron MH, Joux J, Bezard E, Martin-Negrier ML, *et al.* The nigrostriatal pathway in Creutzfeldt-Jakob disease. Journal of Neuropathology and Experimental Neurology. 2009; 68: 809–815.

[110] Kovacs GG, Seguin J, Quadrio I, Höftberger R, Kapás I, Streichenberger N, *et al.* Genetic Creutzfeldt-Jakob disease associated with the E200K mutation: characterization of a complex proteinopathy. Acta Neuropathologica. 2011; 121: 39–57.

[111] Haïk S, Brandel JP, Sazdovitch V, Delasnerie-Lauprêtre N, Peoc'h K, Laplanche JL, *et al.* Dementia with Lewy bodies in a neuropathologic series of suspected Creutzfeldt-Jakob disease. Neurology. 2000; 55: 1401–1404.

[112] Head MW, Lowrie S, Chohan G, Knight R, Scoones DJ, Ironside JW. Variably protease-sensitive prionopathy in a PRNP codon 129 heterozygous UK patient with co-existing tau, α synuclein and Aβ pathology. Acta Neuropathologica. 2010; 120: 821–823.

[113] Iida T, Doh-ura K, Kawashima T, Abe H, Iwaki T. An atypical case of sporadic Creutzfeldt-Jakob disease with Parkinson's disease. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2001; 21: 294–297.

[114] Miguelez-Rodriguez A, Santos-Juanes J, Vicente-Etxenausia I, Perez de Heredia-Goñi K, Garcia B, Quiros LM, *et al.* Brains with sporadic Creutzfeldt-Jakob disease and copathology showed a prolonged end-stage of disease. Journal of Clinical Pathology. 2018; 71: 446–450.

[115] Katorcha E, Makarava N, Lee YJ, Lindberg I, Monteiro MJ, Kovacs GG, *et al.* Cross-seeding of prions by aggregated α-synuclein leads to transmissible spongiform encephalopathy. PLoS Pathogens. 2017; 13: e1006563.

[116] Yamashita S, Sakashita N, Yamashita T, Tawara N, Tasaki M, Kawakami K, *et al.* Concomitant accumulation of α-synuclein and TDP-43 in a patient with corticobasal degeneration. Journal of Neurology. 2014; 261: 2209–2217.

[117] Kasanuki K, Josephs KA, Ferman TJ, Murray ME, Koga S, Konno T, *et al.* Diffuse Lewy body disease manifesting as corticobasal syndrome: A rare form of Lewy body disease. Neurology. 2018; 91: e268–e279.

[118] Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, *et al.* Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain: a Journal of Neurology. 2010; 133: 2045–2057.

[119] Horoupian DS, Wasserstein PH. Alzheimer's disease pathology in motor cortex in dementia with Lewy bodies clinically mimicking corticobasal degeneration. Acta Neuropathologica. 1999; 98: 317–322.

[120] Tsuboi Y, Ahlskog JE, Apaydin H, Parisi JE, Dickson DW.

Lewy bodies are not increased in progressive supranuclear palsy compared with normal controls. Neurology. 2001; 57: 1675–1678.

[121] Mori H, Oda M, Komori T, Arai N, Takanashi M, Mizutani T, *et al.* Lewy bodies in progressive supranuclear palsy. Acta Neuropathologica. 2002; 104: 273–278.

[122] Gearing M, Olson DA, Watts RL, Mirra SS. Progressive supranuclear palsy: neuropathologic and clinical heterogeneity. Neurology. 1994; 44: 1015–1024.

[123] Uchikado H, DelleDonne A, Ahmed Z, Dickson DW. Lewy bodies in progressive supranuclear palsy represent an independent disease process. Journal of Neuropathology and Experimental Neurology. 2006; 65: 387–395.

[124] Judkins AR, Forman MS, Uryu K, Hinkle DA, Asbury AK, Lee VMY, *et al.* Co-occurrence of Parkinson's disease with progressive supranuclear palsy. Acta Neuropathologica. 2002; 103: 526–530.

[125] Wilhelmsen KC, Forman MS, Rosen HJ, Alving LI, Goldman J, Feiger J, *et al.* 17q-linked frontotemporal dementia-amyotrophic lateral sclerosis without tau mutations with tau and alpha-synuclein inclusions. Archives of Neurology. 2004; 61: 398–406.

[126] Seelaar H, Schelhaas HJ, Azmani A, Küsters B, Rosso S, Majoor-Krakauer D, *et al.* TDP-43 pathology in familial frontotemporal dementia and motor neuron disease without Progranulin mutations. Brain: a Journal of Neurology. 2007; 130: 1375–1385.

[127] Yaguchi M, Okamoto K, Nakazato Y. Frontotemporal dementia with cerebral intraneuronal ubiquitin-positive inclusions but lacking lower motor neuron involvement. Acta Neuropathologica. 2003; 105: 81–85.

[128] Helferich AM, Ruf WP, Grozdanov V, Freischmidt A, Feiler MS, Zondler L, *et al.* α-synuclein interacts with SOD1 and promotes its oligomerization. Molecular Neurodegeneration. 2015; 10: 66.

[129] Doherty MJ, Bird TD, Leverenz JB. Alpha-synuclein in motor neuron disease: an immunohistologic study. Acta Neuropathologica. 2004; 107: 169–175.

[130] Noda K, Katayama S, Watanabe C, Yamamura Y, Nakamura S, Yonehara S, *et al.* Pure autonomic failure with motor neuron disease: report of a clinical study and postmortem examination of a patient. Journal of Neurology, Neurosurgery, and Psychiatry. 1996; 60: 351–352.

[131] Mezey E, Dehejia A, Harta G, Papp MI, Polymeropoulos MH, Brownstein MJ. Alpha synuclein in neurodegenerative disorders: murderer or accomplice? Nature Medicine. 1998; 4: 755–757.

[132] Chung YH, Joo KM, Kim MJ, Cha CI. Immunohistochemical study on the distribution of alpha-synuclein in the central nervous system of transgenic mice expressing a human Cu/Zn superoxide dismutase mutation. Neuroscience Letters. 2003; 342: 151–154.

[133] Takei YI, Oguchi K, Koshihara H, Hineno A, Nakamura A, Ohara S. α-Synuclein coaggregation in familial amyotrophic lateral sclerosis with SOD1 gene mutation. Human Pathology. 2013; 44: 1171–1176.

[134] Yang EJ, Choi SM. α -Synuclein Modification in an ALS Animal Model. Evidence-based Complementary and Alternative Medicine: ECAM. 2013; 2013: 259381.

[135] Kim SH, Jung SY, Lee KW, Lee SH, Cai M, Choi SM, *et al.* Bee venom effects on ubiquitin proteasome system in hSOD1(G85R)-expressing NSC34 motor neuron cells. BMC Complementary and Alternative Medicine. 2013; 13: 179.

[136] Koch Y, Helferich AM, Steinacker P, Oeckl P, Walther P, Weishaupt JH, *et al.* Aggregated α-Synuclein Increases SOD1 Oligomerization in a Mouse Model of Amyotrophic Lateral

Sclerosis. The American Journal of Pathology. 2016; 186: 2152–2161.

[137] Roberts B, Theunissen F, Mastaglia FL, Akkari PA, Flynn LL. Synucleinopathy in Amyotrophic Lateral Sclerosis: A Potential Avenue for Antisense Therapeutics? International Journal of Molecular Sciences. 2022; 23: 9364.

[138] Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, *et al*. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain: a Journal of Neurology. 2018; 141: 2181–2193.

[139] Visanji NP, Lang AE, Kovacs GG. Beyond the synucleinopathies: alpha synuclein as a driving force in neurodegenerative comorbidities. Translational Neurodegeneration. 2019; 8: 28.

[140] Irwin DJ, Lee VMY, Trojanowski JQ. Parkinson's disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies. Nature Reviews. Neuroscience. 2013; 14: 626–636.

[141] Aoki S, Liu AW, Zucca A, Zucca S, Wickens JR. Role of Striatal Cholinergic Interneurons in Set-Shifting in the Rat. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2015; 35: 9424–9431.

[142] Moussaud S, Jones DR, Moussaud-Lamodière EL, Delenclos M, Ross OA, McLean PJ. Alpha-synuclein and tau: teammates in neurodegeneration? Molecular Neurodegeneration. 2014; 9: 43.

[143] Nonaka T, Masuda-Suzukake M, Hasegawa M. Molecular mechanisms of the co-deposition of multiple pathological proteins in neurodegenerative diseases. Neuropathology: Official Journal of the Japanese Society of Neuropathology. 2018; 38: 64–71.

[144] Jamerlan AM, An SSA. A Microplate-Based Approach to Map Interactions between TDP-43 and α-Synuclein. Journal of Clinical Medicine. 2022; 11: 573.

[145] Dhakal S, Wyant CE, George HE, Morgan SE, Rangachari V. Prion-like C-Terminal Domain of TDP-43 and α-Synuclein Interact Synergistically to Generate Neurotoxic Hybrid Fibrils. Journal of Molecular Biology. 2021; 433: 166953.

[146] Markesbery WR, Jicha GA, Liu H, Schmitt FA. Lewy body pathology in normal elderly subjects. Journal of Neuropathology and Experimental Neurology. 2009; 68: 816–822.

[147] Zolochevska O, Taglialatela G. Non-Demented Individuals with Alzheimer's Disease Neuropathology: Resistance to Cognitive Decline May Reveal New Treatment Strategies. Current Pharmaceutical Design. 2016; 22: 4063–4068.

[148] Espay AJ, Vizcarra JA, Marsili L, Lang AE, Simon DK, Merola A, *et al*. Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases. Neurology. 2019; 92: 329–337.

[149] Maderna E, Cattaneo C, Cacciatore F, Catania M, Di Fede G, Tagliavini F, *et al*. Divergent cognitive status with the same Braak stage of neurofibrillary pathology: does the pattern of amyloid-β deposits make the difference? Journal of Alzheimer's Disease: JAD. 2015; 43: 375–379.

[150] Armstrong RA. beta-Amyloid (A beta) deposition in elderly non-demented patients and patients with Alzheimer's disease. Neuroscience Letters. 1994; 178: 59–62.

[151] Beker N, Ganz A, Hulsman M, Klausch T, Schmand BA, Scheltens P, *et al*. Association of Cognitive Function Trajectories in Centenarians With Postmortem Neuropathology, Physical Health, and Other Risk Factors for Cognitive Decline. JAMA Network Open. 2021; 4: e2031654.

[152] Ganz AB, Beker N, Hulsman M, Sikkes S, Netherlands Brain Bank, Scheltens P, *et al*. Neuropathology and cognitive performance in self-reported cognitively healthy centenarians. Acta Neuropathologica Communications. 2018; 6: 64.

[153] Mormino EC, Papp KV. Amyloid Accumulation and Cognitive Decline in Clinically Normal Older Individuals: Implications for Aging and Early Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2018; 64: S633–S646.

[154] Rumble B, Retallack R, Hilbich C, Simms G, Multhaup G, Martins R, *et al*. Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. The New England Journal of Medicine. 1989; 320: 1446–1452.

[155] Webb RL, Murphy MP. β-Secretases, Alzheimer's Disease, and Down Syndrome. Current Gerontology and Geriatrics Research. 2012; 2012: 362839.

[156] Holland AJ, Hon J, Huppert FA, Stevens F. Incidence and course of dementia in people with Down's syndrome: findings from a population-based study. Journal of Intellectual Disability Research: JIDR. 2000; 44: 138–146.

[157] McCarron M, McCallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. Journal of Intellectual Disability Research: JIDR. 2017; 61: 843–852.

[158] Lott IT, Head E. Dementia in Down syndrome: unique insights for Alzheimer disease research. Nature Reviews. Neurology. 2019; 15: 135–147.

[159] Grigorova M, Mak E, Brown SSG, Beresford-Webb J, Hong YT, Fryer TD, *et al*. Amyloid- β and tau deposition influences cognitive and functional decline in Down syndrome. Neurobiology of Aging. 2022; 119: 36–45.

[160] Donaghy PC, Firbank MJ, Thomas AJ, Lloyd J, Petrides G, Barnett N, *et al*. Clinical and imaging correlates of amyloid deposition in dementia with Lewy bodies. Movement Disorders: Official Journal of the Movement Disorder Society. 2018; 33: 1130–1138.

[161] Biundo R, Weis L, Fiorenzato E, Pistonesi F, Cagnin A, Bertoldo A, *et al*. The contribution of beta-amyloid to dementia in Lewy body diseases: a 1-year follow-up study. Brain Communications. 2021; 3: fcab180.

[162] Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RKB. Striatal beta-amyloid deposition in Parkinson disease with dementia. Journal of Neuropathology and Experimental Neurology. 2008; 67: 155–161.

[163] Kalaitzakis ME, Pearce RKB, Gentleman SM. Clinical correlates of pathology in the claustrum in Parkinson's disease and dementia with Lewy bodies. Neuroscience Letters. 2009; 461: 12–15.

[164] Lim EW, Aarsland D, Ffytche D, Taddei RN, van Wamelen DJ, Wan YM, *et al*. Amyloid-β and Parkinson's disease. Journal of Neurology. 2019; 266: 2605–2619.

[165] Melzer TR, Stark MR, Keenan RJ, Myall DJ, MacAskill MR, Pitcher TL, *et al*. Beta Amyloid Deposition Is Not Associated With Cognitive Impairment in Parkinson's Disease. Frontiers in Neurology. 2019; 10: 391.

[166] Mihaescu AS, Valli M, Uribe C, Diez-Cirarda M, Masellis M, Graff-Guerrero A, *et al*. Beta amyloid deposition and cognitive decline in Parkinson's disease: a study of the PPMI cohort. Molecular Brain. 2022; 15: 79.

[167] Piras IS, Bleul C, Schrauwen I, Talboom J, Llaci L, De Both MD, *et al*. Transcriptional profiling of multiple system atrophy cerebellar tissue highlights differences between the parkinsonian and cerebellar sub-types of the disease. Acta Neuropathologica Communications. 2020; 8: 76.

[168] Armstrong RA. Density and spatial pattern of β-amyloid (Aβ) deposits in corticobasal degeneration. Folia Neuropathologica. 2011; 49: 14–20.

[169] Armstrong RA. The interface between Alzheimer's disease, normal aging, and related disorders. Current Aging Science. 2008; 1: 122–132.

[170] Armstrong RA, Lantos PL, Cairns NJ. Overlap between neurodegenerative disorders. Neuropathology: Official Journal of

the Japanese Society of Neuropathology. 2005; 25: 111–124.

[171] Schneider JA, Watts RL, Gearing M, Brewer RP, Mirra SS. Corticobasal degeneration: neuropathologic and clinical heterogeneity. Neurology. 1997; 48: 959–969.

[172] Debatin L, Streffer J, Geissen M, Matschke J, Aguzzi A, Glatzel M. Association between deposition of beta-amyloid and pathological prion protein in sporadic Creutzfeldt-Jakob disease. Neuro-degenerative Diseases. 2008; 5: 347–354.

[173] Bujan B, Hofer MJ, Oertel WH, Pagenstecher A, Bürk K. Multiple system atrophy of the cerebellar type (MSA-C) with concomitant beta-amyloid and tau pathology. Clinical Neuropathology. 2013; 32: 286–290.

[174] Matrone C. The paradigm of amyloid precursor protein in amyotrophic lateral sclerosis: The potential role of the _682YENPTY_687 motif. Computational and Structural Biotechnology Journal. 2023; 21: 923–930.

[175] Yoon EJ, Park HJ, Kim GY, Cho HM, Choi JH, Park HY, et al. Intracellular amyloid beta interacts with SOD1 and impairs the enzymatic activity of SOD1: implications for the pathogenesis of amyotrophic lateral sclerosis. Experimental & Molecular Medicine. 2009; 41: 611–617.

[176] Vargas-George S, Dave KR. Models of cerebral amyloid angiopathy-related intracerebral hemorrhage. Brain Hemorrhages. 2022; 3: 189–199.

[177] Weber SA, Patel RK, Lutsep HL. Cerebral amyloid angiopathy: diagnosis and potential therapies. Expert Review of Neurotherapeutics. 2018; 18: 503–513.

[178] Raposo N, Viguier A, Cuvinciuc V, Calviere L, Cognard C, Bonneville F, et al. Cortical subarachnoid haemorrhage in the elderly: a recurrent event probably related to cerebral amyloid angiopathy. European Journal of Neurology. 2011; 18: 597–603.

[179] Charidimou A, Boulouis G, Gurol ME, Ayata C, Bacskai BJ, Frosch MP, et al. Emerging concepts in sporadic cerebral amyloid angiopathy. Brain: a Journal of Neurology. 2017; 140: 1829–1850.

[180] Cordonnier C, van der Flier WM. Brain microbleeds and Alzheimer's disease: innocent observation or key player? Brain: a Journal of Neurology. 2011; 134: 335–344.

[181] Yates PA, Desmond PM, Phal PM, Steward C, Szoeke C, Salvado O, et al. Incidence of cerebral microbleeds in preclinical Alzheimer disease. Neurology. 2014; 82: 1266–1273.

[182] Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nature Reviews. Neurology. 2020; 16: 30–42.

[183] Ghetti B, Piccardo P, Frangione B, Bugiani O, Giaccone G, Young K, et al. Prion protein amyloidosis. Brain Pathology (Zurich, Switzerland). 1996; 6: 127–145.

[184] Ghetti B, Dlouhy SR, Giaccone G, Bugiani O, Frangione B, Farlow MR, et al. Gerstmann-Sträussler-Scheinker disease and the Indiana kindred. Brain Pathology (Zurich, Switzerland). 1995; 5: 61–75.

[185] Giaccone G, Mangieri M, Capobianco R, Limido L, Hauw JJ, Haïk S, et al. Tauopathy in human and experimental variant Creutzfeldt-Jakob disease. Neurobiology of Aging. 2008; 29: 1864–1873.

[186] Kovacs GG, Rahimi J, Ströbel T, Lutz MI, Regelsberger G, Streichenberger N, et al. Tau pathology in Creutzfeldt-Jakob disease revisited. Brain Pathology (Zurich, Switzerland). 2017; 27: 332–344.

[187] Ghetti B, Tagliavini F, Giaccone G, Bugiani O, Frangione B, Farlow MR, et al. Familial Gerstmann-Sträussler-Scheinker disease with neurofibrillary tangles. Molecular Neurobiology. 1994; 8: 41–48.

[188] Wills J, Jones J, Haggerty T, Duka V, Joyce JN, Sidhu A. Elevated tauopathy and alpha-synuclein pathology in postmortem Parkinson's disease brains with and without dementia. Experimental Neurology. 2010; 225: 210–218.

[189] Montalbano M, Majmundar L, Sengupta U, Fung L, Kayed R. Pathological tau signatures and nuclear alterations in neurons, astrocytes and microglia in Alzheimer's disease, progressive supranuclear palsy, and dementia with Lewy bodies. Brain Pathology (Zurich, Switzerland). 2023; 33: e13112.

[190] Colom-Cadena M, Gelpi E, Charif S, Belbin O, Blesa R, Martí MJ, et al. Confluence of α-synuclein, tau, and β-amyloid pathologies in dementia with Lewy bodies. Journal of Neuropathology and Experimental Neurology. 2013; 72: 1203–1212.

[191] Piao YS, Hayashi S, Hasegawa M, Wakabayashi K, Yamada M, Yoshimoto M, et al. Co-localization of alpha-synuclein and phosphorylated tau in neuronal and glial cytoplasmic inclusions in a patient with multiple system atrophy of long duration. Acta Neuropathologica. 2001; 101: 285–293.

[192] Badiola N, de Oliveira RM, Herrera F, Guardia-Laguarta C, Gonçalves SA, Pera M, et al. Tau enhances α-synuclein aggregation and toxicity in cellular models of synucleinopathy. PloS one. 2011; 6: e26609.

[193] Pan L, Li C, Meng L, Tian Y, He M, Yuan X, et al. Tau accelerates α-synuclein aggregation and spreading in Parkinson's disease. Brain: a Journal of Neurology. 2022; 145: 3454–3471.

[194] Yang W, Ang LC, Strong MJ. Tau protein aggregation in the frontal and entorhinal cortices as a function of aging. Brain Research. Developmental Brain Research. 2005; 156: 127–138.

[195] Buée-Scherrer V, Buée L, Hof PR, Leveugle B, Gilles C, Loerzel AJ, et al. Neurofibrillary degeneration in amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam. Immunochemical characterization of tau proteins. The American Journal of Pathology. 1995; 146: 924–932.

[196] Vidal R, Calero M, Piccardo P, Farlow MR, Unverzagt FW, Méndez E, et al. Senile dementia associated with amyloid beta protein angiopathy and tau perivascular pathology but not neuritic plaques in patients homozygous for the APOE-epsilon4 allele. Acta Neuropathologica. 2000; 100: 1–12.

[197] You Y, Perkins A, Cisternas P, Muñoz B, Taylor X, You Y, et al. Tau as a mediator of neurotoxicity associated to cerebral amyloid angiopathy. Acta Neuropathologica Communications. 2019; 7: 26.

[198] St-Amour I, Turgeon A, Goupil C, Planel E, Hébert SS. Co-occurrence of mixed proteinopathies in late-stage Huntington's disease. Acta Neuropathologica. 2018; 135: 249–265.

[199] Liu P, Smith BR, Huang ES, Mahesh A, Vonsattel JPG, Petersen AJ, et al. A soluble truncated tau species related to cognitive dysfunction and caspase-2 is elevated in the brain of Huntington's disease patients. Acta Neuropathologica Communications. 2019; 7: 111.

[200] Petry S, Nateghi B, Keraudren R, Sergeant N, Planel E, Hébert SS, et al. Differential Regulation of Tau Exon 2 and 10 Isoforms in Huntington's Disease Brain. Neuroscience. 2023; 518: 54–63.

[201] Fernández-Nogales M, Cabrera JR, Santos-Galindo M, Hoozemans JJM, Ferrer I, Rozemuller AJM, et al. Huntington's disease is a four-repeat tauopathy with tau nuclear rods. Nature Medicine. 2014; 20: 881–885.

[202] Delacourte A, David JP, Sergeant N, Buée L, Wattez A, Vermersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology. 1999; 52: 1158–1165.

[203] Nonaka T, Hasegawa M. Prion-like properties of assembled TDP-43. Current Opinion in Neurobiology. 2020; 61: 23–28.

[204] Geuens T, Bouhy D, Timmerman V. The hnRNP family: insights into their role in health and disease. Human Genetics. 2016; 135: 851–867.

[205] Kim HJ, Taylor JP. Lost in Transportation: Nucleocytoplasmic

Transport Defects in ALS and Other Neurodegenerative Diseases. Neuron. 2017; 96: 285–297.

[206] Tziortzouda P, Van Den Bosch L, Hirth F. Triad of TDP43 control in neurodegeneration: autoregulation, localization and aggregation. Nature Reviews. Neuroscience. 2021; 22: 197–208.

[207] Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Annals of Neurology. 2007; 61: 435–445.

[208] Meneses A, Koga S, O'Leary J, Dickson DW, Bu G, Zhao N. TDP-43 Pathology in Alzheimer's Disease. Molecular Neurodegeneration. 2021; 16: 84.

[209] Josephs KA, Whitwell JL, Weigand SD, Murray ME, Tosakulwong N, Liesinger AM, et al. TDP-43 is a key player in the clinical features associated with Alzheimer's disease. Acta Neuropathologica. 2014; 127: 811–824.

[210] Josephs KA, Whitwell JL, Tosakulwong N, Weigand SD, Murray ME, Liesinger AM, et al. TAR DNA-binding protein 43 and pathological subtype of Alzheimer's disease impact clinical features. Annals of Neurology. 2015; 78: 697–709.

[211] Josephs KA, Murray ME, Whitwell JL, Tosakulwong N, Weigand SD, Petrucelli L, et al. Updated TDP-43 in Alzheimer's disease staging scheme. Acta Neuropathologica. 2016; 131: 571–585.

[212] Guerrero-Muñoz MJ, Castillo-Carranza DL, Krishnamurthy S, Paulucci-Holthauzen AA, Sengupta U, Lasagna-Reeves CA, et al. Amyloid-β oligomers as a template for secondary amyloidosis in Alzheimer's disease. Neurobiology of Disease. 2014; 71: 14–23.

[213] Shih YH, Tu LH, Chang TY, Ganesan K, Chang WW, Chang PS, et al. TDP-43 interacts with amyloid-β, inhibits fibrillization, and worsens pathology in a model of Alzheimer's disease. Nature Communications. 2020; 11: 5950.

[214] Koper MJ, Tomé SO, Gawor K, Belet A, Van Schoor E, Schaeverbeke J, et al. LATE-NC aggravates GVD-mediated necroptosis in Alzheimer's disease. Acta Neuropathologica Communications. 2022; 10: 128.

[215] Koga S, Sanchez-Contreras M, Josephs KA, Uitti RJ, Graff-Radford N, van Gerpen JA, et al. Distribution and characteristics of transactive response DNA binding protein 43 kDa pathology in progressive supranuclear palsy. Movement Disorders: Official Journal of the Movement Disorder Society. 2017; 32: 246–255.

[216] Riku Y, Iwasaki Y, Ishigaki S, Akagi A, Hasegawa M, Nishioka K, et al. Motor neuron TDP-43 proteinopathy in progressive supranuclear palsy and corticobasal degeneration. Brain: a Journal of Neurology. 2022; 145: 2769–2784.

[217] Koga S, Kouri N, Walton RL, Ebbert MTW, Josephs KA, Litvan I, et al. Corticobasal degeneration with TDP-43 pathology presenting with progressive supranuclear palsy syndrome: a distinct clinicopathologic subtype. Acta Neuropathologica. 2018; 136: 389–404.

[218] Uryu K, Nakashima-Yasuda H, Forman MS, Kwong LK, Clark CM, Grossman M, et al. Concomitant TAR-DNA-binding protein 43 pathology is present in Alzheimer disease and corticobasal degeneration but not in other tauopathies. Journal of Neuropathology and Experimental Neurology. 2008; 67: 555–564.

[219] Robinson AC, Thompson JC, Weedon L, Rollinson S, Pickering-Brown S, Snowden JS, et al. No interaction between tau and TDP-43 pathologies in either frontotemporal lobar degeneration or motor neurone disease. Neuropathology and Applied Neurobiology. 2014; 40: 844–854.

[220] Schwab C, Arai T, Hasegawa M, Yu S, McGeer PL. Colocalization of transactivation-responsive DNA-binding protein 43 and huntingtin in inclusions of Huntington disease. Journal of Neuropathology and Experimental Neurology. 2008; 67: 1159–

1165.

[221] Maat-Schieman M, Roos R, Losekoot M, Dorsman J, Welling-Graafland C, Hegeman-Kleinn I, et al. Neuronal intranuclear and neuropil inclusions for pathological assessment of Huntington's disease. Brain Pathology (Zurich, Switzerland). 2007; 17: 31–37.

[222] Kegel KB, Meloni AR, Yi Y, Kim YJ, Doyle E, Cuiffo BG, et al. Huntingtin is present in the nucleus, interacts with the transcriptional corepressor C-terminal binding protein, and represses transcription. The Journal of Biological Chemistry. 2002; 277: 7466–7476.

[223] Koga S, Lin WL, Walton RL, Ross OA, Dickson DW. TDP-43 pathology in multiple system atrophy: colocalization of TDP-43 and α-synuclein in glial cytoplasmic inclusions. Neuropathology and Applied Neurobiology. 2018; 44: 707–721.

[224] Nakashima-Yasuda H, Uryu K, Robinson J, Xie SX, Hurtig H, Duda JE, et al. Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. Acta Neuropathologica. 2007; 114: 221–229.

[225] McAleese KE, Walker L, Erskine D, Thomas AJ, McKeith IG, Attems J. TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing. Brain Pathology (Zurich, Switzerland). 2017; 27: 472–479.

[226] Arai T, Mackenzie IRA, Hasegawa M, Nonoka T, Niizato K, Tsuchiya K, et al. Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. Acta Neuropathologica. 2009; 117: 125–136.

[227] Outeiro TF, Koss DJ, Erskine D, Walker L, Kurzawa-Akanbi M, Burn D, et al. Dementia with Lewy bodies: an update and outlook. Molecular Neurodegeneration. 2019; 14: 5.

[228] Higashi S, Iseki E, Yamamoto R, Minegishi M, Hino H, Fujisawa K, et al. Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. Brain Research. 2007; 1184: 284–294.

[229] Yokota O, Davidson Y, Arai T, Hasegawa M, Akiyama H, Ishizu H, et al. Effect of topographical distribution of α-synuclein pathology on TDP-43 accumulation in Lewy body disease. Acta Neuropathologica. 2010; 120: 789–801.

[230] Tian T, Huang C, Tong J, Yang M, Zhou H, Xia XG. TDP-43 potentiates alpha-synuclein toxicity to dopaminergic neurons in transgenic mice. International Journal of Biological Sciences. 2011; 7: 234–243.

[231] Shen L, Wang C, Chen L, Leung KL, Lo E, Lakso M, et al. TDP-1/TDP-43 potentiates human α-Synuclein (HASN) neurodegeneration in Caenorhabditis elegans. Biochimica et Biophysica Acta. Molecular Basis of Disease. 2020; 1866: 165876.

[232] Fujishiro H, Uchikado H, Arai T, Hasegawa M, Akiyama H, Yokota O, et al. Accumulation of phosphorylated TDP-43 in brains of patients with argyrophilic grain disease. Acta Neuropathologica. 2009; 117: 151–158.

[233] Koga S, Murakami A, Martin NB, Dickson DW. The frequency and distribution of TDP-43 pathology in argyrophilic grain disease. Journal of Neuropathology and Experimental Neurology. 2023; 82: 739–741.

[234] Arnold SJ, Dugger BN, Beach TG. TDP-43 deposition in prospectively followed, cognitively normal elderly individuals: correlation with argyrophilic grains but not other concomitant pathologies. Acta Neuropathologica. 2013; 126: 51–57.

[235] Nascimento C, Suemoto CK, Rodriguez RD, Alho ATDL, Leite RP, Farfel JM, et al. Higher Prevalence of TDP-43 Proteinopathy in Cognitively Normal Asians: A Clinicopathological Study on a Multiethnic Sample. Brain Pathology (Zurich, Switzerland). 2016; 26: 177–185.

[236] Spires-Jones TL, Attems J, Thal DR. Interactions of pathological proteins in neurodegenerative diseases. Acta Neuropathologica. 2017; 134: 187–205.