

Review

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

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Academic Editor: Antoni Camins

Submitted: 28 July 2023 Revised: 21 August 2023 Accepted: 26 September 2023 Published: 20 October 2023

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 ($A\beta$) 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, $A\beta$ 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 strategies.

Keywords: neurodegeneration; protein aggregation; biomarker; neuropathology; tauopathies; 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 exist 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 ($A\beta$) and tau are the main hallmarks of AD: $A\beta$ 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]. $A\beta$ deposition precedes tau aggregation by several years or decades and preclinical studies have shown that $A\beta$ 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 $A\beta$ 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 $A\beta$ deposition in the cortex which increased with age and these findings were in accord with postmortem analyses, which showed an age-dependent increase of $A\beta$ 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 $A\beta$, 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 $A\beta$, 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, $A\beta$, 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-

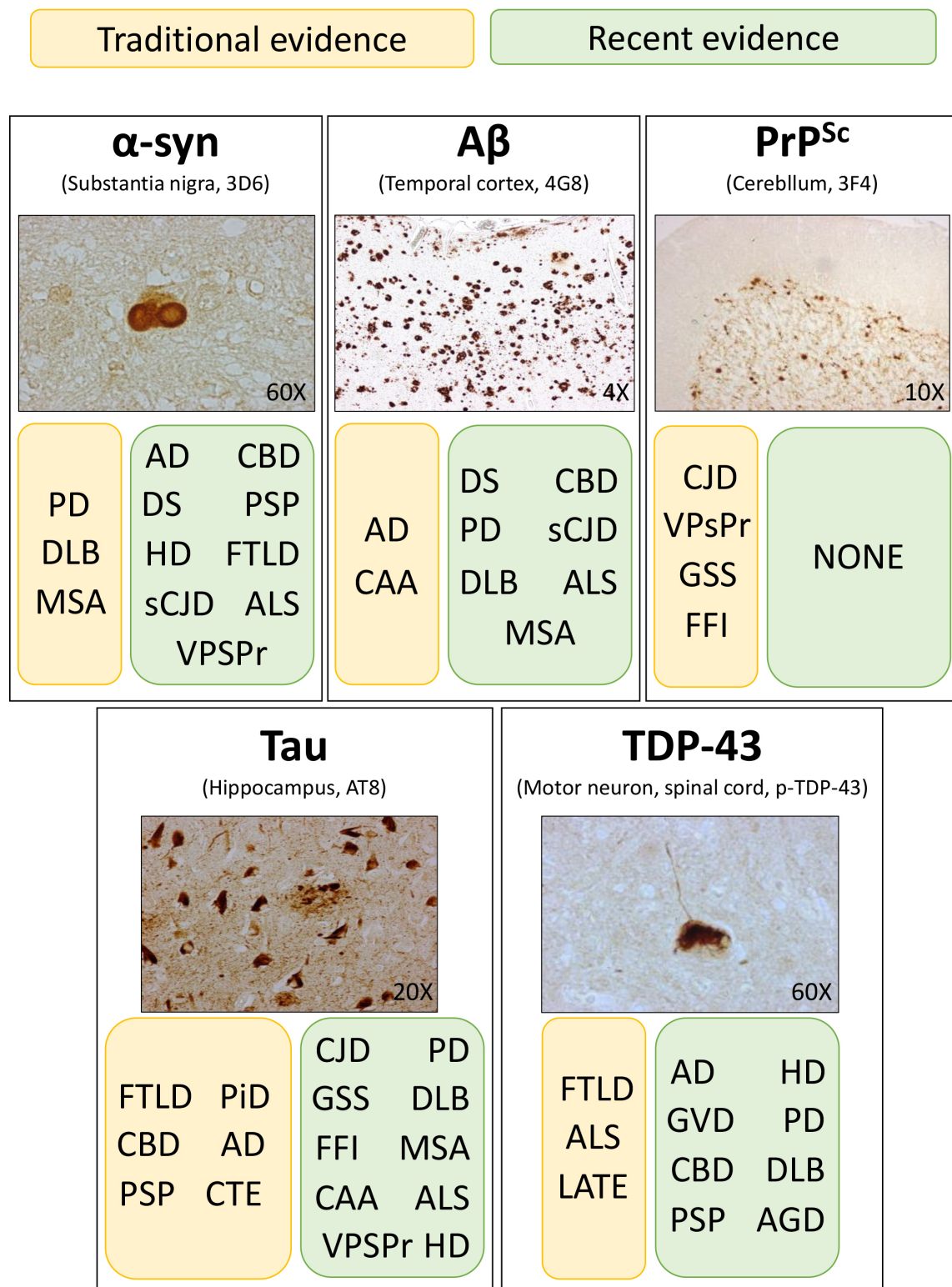


Fig. 1. Schematic representation of the traditional (yellow boxes) and recent (green boxes) evidence regarding protein aggregates in the central nervous system of patients with various neurodegenerative diseases. Histological stains show the typical morphological features of α -synuclein (α -syn), amyloid- β ($A\beta$), 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 amygdala 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 $A\beta$ 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 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, $A\beta$ 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 (~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 (~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

$A\beta$ primarily occur in the brain of AD patients, but they can also occur in some non-AD conditions. For instance, $A\beta$ 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 $A\beta$ 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 $A\beta$ pathology were found in the brains of high performing subjects [151,152]. Therefore, $A\beta$ 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

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

A β 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 A β production [154,155]. As a result, individuals with DS develop A β 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, A β 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 A β were found in the brains of some patients with DLB, suggesting that A β 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 A β 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 A β 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 A β 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 post-mortem, biochemical, and imaging analyses, increasingly indicate the involvement of A β in PD, and recent studies indicate a possible role of A β in gait disturbances and cognitive impairment in PD patients [164]. However, the role of A β in cognitive decline in PD requires further investigations [165,166]. Similarly, deposits of A β 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 A β 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 A β interacts with SOD1 (an enzyme linked to ALS) and this lead to an impaired SOD1 enzymatic activity. Thus, A β may modulate ALS progression [175]. An-

other condition characterized by the presence of A β is the cerebral amyloid angiopathy (CAA), a cerebrovascular disease commonly observed among the elderly [176]. In this case, the deposition of A β 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 A β 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 $A\beta$ 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, FTLTDP 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 $A\beta$ 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); entorhinal 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 $A\beta$ or tau are able to cross-seed the polymerization of TDP-43 into pathological aggregates [212] and TDP-43 may regulate $A\beta$ 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 (~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 FTLTDP [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 huntingtin (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 (~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 interaction 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.

Author Contributions

FM and GG wrote the manuscript and designed the figure. AC, ILD, AL, NC, GB and FAC contributed in manuscript preparation, conceptualization, data analysis and interpretation. All the authors critically reviewed the manuscript and approved its final version.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Given their role as Guest Editor member of FBL, Fabio Moda and Giorgio Giaccone had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Antoni Camins.

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