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Review

Neuropathological and Biomarker Findings in Parkinson's Disease and Alzheimer's Disease: From Protein Aggregates to Synaptic Dysfunction

Yaroslau Compta[a,b,*] and Tamas Revesz[c,d,e,*]
[a]*Parkinson's disease & Movement Disorders Unit, Neurology Service, Hospital Clínic / IDIBAPS / CIBERNED, Barcelona, Catalonia, Spain*
[b]*Institut de Neurociències, Maextu's excellence center, University of Barcelona, Barcelona, Catalonia, Spain*
[c]*Queen Square Brain Bank for Neurological Disorders, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, UK*
[d]*Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology, London, UK*
[e]*Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, UK*

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Abstract.
There is mounting evidence that Parkinson's disease (PD) and Alzheimer's disease (AD) share neuropathological hallmarks, while similar types of biomarkers are being applied to both. In this review we aimed to explore similarities and differences between PD and AD at both the neuropathology and the biomarker levels, specifically focusing on protein aggregates and synapse dysfunction. Thus, amyloid-β peptide (Aβ) and tau lesions of the Alzheimer-type are common in PD and α-synuclein Lewy-type aggregates are frequent findings in AD. Modern neuropathological techniques adding to routine immunohistochemistry might take further our knowledge of these diseases beyond protein aggregates and down to their presynaptic and postsynaptic terminals, with potential mechanistic and even future therapeutic implications. Translation of neuropathological discoveries to the clinic remains challenging. Cerebrospinal fluid (CSF) and positron emission tomography (PET) markers of Aβ and tau have been shown to be reliable for AD diagnosis. Conversely, CSF markers of α-synuclein have not been that consistent. In terms of PET markers, there is no PET probe available for α-synuclein yet, while the AD PET markers range from consistent evidence of their specificity (amyloid imaging) to greater uncertainty of their reliability due to off-target binding (tau imaging). CSF synaptic markers are attractive, still needing more evidence, which currently suggests those might be non-specific markers of disease progression. It can be summarized that there is neuropathological evidence that protein aggregates of AD and PD are present both at the soma and the synapse. Thus, a number of CSF and PET biomarkers beyond α-synuclein, tau and Aβ might capture these different faces of protein-related neurodegeneration. It remains to be seen what the longitudinal outcomes and the potential value as surrogate markers of these biomarkers are.

Keywords: α-Synuclein, alzheimer's disease, amyloid-β, biomarkers, cerebrospinal fluid, lewy-type pathology, molecular imaging, Parkinson's disease, synaptic dysfunction, tau

*Correspondence to: Yaroslau Compta, Parkinson's disease & Movement Disorders Unit, Neurology Service, Hospital Clínic / IDIBAPS / CIBERNED, Barcelona, Catalonia, Spain. E-mail: YCOMPTA@clinic.cat. and Tamas Revesz, Queen Square Brain Bank for Neurological Disorders, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, UK. E-mail: t.revesz@ucl.ac.uk.

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INTRODUCTION

Partly derived from the fact that dementia is very common in Parkinson's disease (PD) [1], there is mounting neuropathological evidence that PD and Alzheimer's disease (AD) share several common features [2, 3]. Traditional post-mortem neuropathological studies are nowadays supplemented by biomarker studies purportedly reflecting the underlying pathology *in vivo*, ranging from biochemical studies in cerebrospinal fluid (CSF) to molecular imaging of proteins deposition such as amyloid-β (Aβ) or tau. Both types of studies have favoured in recent years the notion that neurofibrillary tangle-type lesions composed of hyperphosphorylated tau and, particularly, Aβ-containing aggregates are common in PD and associated with presence and risk of, as well as timing to, dementia [2, 3]. All this has supposed a paradigm shift of sorts, departing from the general conception at the end of the 20th and early 21st century that cortical Lewy pathology alone accounted for dementia in PD, to conceiving that both Lewy and Alzheimer pathologies are relevant in PD-dementia. Additionally, there is also consistent data as to the concomitant presence of α-synuclein containing Lewy-type aggregates in a significant proportion of both sporadic and familial AD, particularly in the amygdala [4, 5].

However, it remains unknown what is the exact mechanistic role of co-existing Lewy and Alzheimer pathologies observed in post-mortem studies, with common criticism being that these most often reflect findings in end-stage cases (unless the autopsies are performed in patients dying prematurely of an unrelated illness) and that these may not necessarily reflect what originally drove the symptoms (in this case more importantly, but not exclusively, dementia).

As for *in vivo* biomarker studies-derived evidence of coexistence of both Lewy and Alzheimer pathologies it is yet controversial as it is still not clear whether the used biomarkers actually reflect underlying pathology or rather are the consequence of some other molecular processes. Thus, in studies assessing CSF biomarkers, the main concern is that these might be reflecting non-specific alterations (mostly axonal loss or neuronal degeneration, in the case of tau [6]) or intrinsic processes related to the soluble species of the involved protein (such as synaptic dysfunction in the case of Aβ [7] and α-synuclein [8]), rather than the respective disease protein aggregates.

Here we revisit the neuropathological and biomarker evidence from recent years focusing in pathology and synaptic dysfunction related to PD and AD-related disease proteins (α-synuclein, Aβ and tau), in order to put these in perspective and suggest future directions.

NEUROPATHOLOGICAL EVIDENCE OF ASSOCIATION OF ALZHEIMER'S DISEASE-TYPE PATHOLOGY WITH LEWY PATHOLOGY IN PARKINSON'S DISEASE

In the pre-α-synuclein era when assessment of cortical Lewy bodies was possible, but more difficult and less reliable, some studies found Alzheimer-type lesions as a correlate of dementia in PD [9–12]. With the discovery of α-synuclein as a key component of Lewy bodies, Lewy neurites and other lesion types [13] the subsequent introduction of α-synuclein immunohistochemistry, the tide turned, and several studies favoured cortical Lewy pathology as the main (and almost sole) neuropathological correlate of cognitive dysfunction in PD. However, in the last decade, a number of clinico-pathological studies consistently showed that Alzheimer co-pathology is significantly associated with cognitive dysfunction in PD, both in terms of increased risk and shorter time interval from disease onset to the development of dementia. All these studies have been extensively reviewed [2, 3] and are summarized in Table 1 [9–32]. In short, large studies have identified that, besides cortical Lewy-type pathology, Aβ plaque pathology is a determinant of cognitive impairment in PD as Aβ deposition has been shown to be associated with the risk and timing of developing dementia [22, 28, 29] and with disease duration [30]. Others have identified tau pathology as the determinant of progression to dementia [32]. These discrepancies as to the predominating role of Aβ or tau most probably owe to methodological differences (for instance, including all Aβ plaque forms, such as diffuse and mature plaques [25, 27], vs. only accounting neuritic plaques as Aβ pathology [31]).

NEUROPATHOLOGICAL EVIDENCE OF CO-EXISTING LEWY-TYPE LESIONS IN ALZHEIMER'S DISEASE

Similar to co-existing AD-type pathology in PD, Lewy-type pathology has also been widely studied in AD. Interestingly, the relationship between Lewy pathology and AD attracted the interest of investigators before the actual finding of specific Lewy

Table 1
Summary of relevant neuropathological evidence of Alzheimer-type co-pathology in Parkinson's disease ranging from few pre-α-synuclein era examples to more recent clinicopathological studies

Reference	*Year*	*Sample*	*Main outcomes*	*Main findings*	*Comments*
Hakim & Mathieson [9]	1979	34 PD	Dementia cases Plaques & tangles	19 PDD cases (56%) 33 PD cases with plaques & tangles	
Boller et al. [10]	1980	36 PD cases (29 with adequate clinical data)	Dementia cases Plaques & tangles	9 cases with severe dementia (31%) 7 cases with mild dementia (24%) Plaques & tangles in 15/36 (42%): →9/9 (100%) with severe dementia →3/7 (43%) with mild dementia →3/13 (23%) with no dementia AD changes = 6-fold in PD (33&) relative to controls (5.1%) AD changes = shorter survival than no AD changes	• Retrospective • Pre-α-synuclein era study (ubiquitin immune-staining)
Jendroska et al. [11]	1996	50 PD cases 79 controls	Dementia cases Plaques & tangles Vascular damage Hydrocephalus	23 patients had dementia including all 9 cases with widespread cortical Aβ 5 of 17 controls with widespread cortical Aβwere not demented 14 patients with dementia unrelated to Aβ → 5 = not explained by histological changes → 4 = vascular damage → 3 = numerous cortical Lewy bodies → 2 = hydrocephalus	• Definition of dementia?
Mattila et al. [12]	1998	44 PD cases	CERAD neuropathological assessment Reisberg's global deterioration scale (GDS) Lewy & Alzheimer-changes in the substantia nigra, amygdala, hippocampus and cortex	At least 1 cortical Lewy body in 93% 43% of cases with Alzheimer-changes Total cortical Lewy bodies+temporal neurofibrillary tangles associated with cognitive impairment	
Mattila et al. [14]	2000	45 PD cases	Amygdala, hippocampus+6 cortical gyri Lewy body and Alzheimer type changes	At least 1 cortical Lewy body in 95% 40% of cases with Alzheimer-changes Lewy bodies density correlated with plaques rather than tangles Frontal Lewy bodies = significant predictor of cognitive impairment	• Retrospective • α-synuclein immunostaining
Hurtig et al. [15]	2000	20 PDND 22 PDD	α-synuclein, ubiquitin and thioflavine S stainings	α-synuclein+cortical Lewy bodies → highly sensitive (91%) and specific (90%) neuropathologic markers of dementia in PD Slightly more sensitive than ubiquitin+cortical Lewy bodies Better indicators of dementia than angles, plaques, or dystrophic neurites.	

Table 1
Continued

Reference	*Year*	*Sample*	*Main outcomes*	*Main findings*	*Comments*
Apaydin et al. [16]	2002	9 PDND 12 PDD	Hematoxylin-eosin, Bielschowsky and thioflavin S stains+α-synuclein and tau immunostainings	12 PDD → diffuse or transitional Lewy bodies Mean cortical & limbic Lewy body counts 10-fold greater in PDD > PDND Cortical Lewy body counts significantly correlated to plaques & tangles	
Colosimo et al. [17]	2005	38 PD (21 = cognitive impairment)	α-synuclein and tau immunostainings	Of the 17 patients without cognitive impairment, 9 had transitional and 8 had neocortical Lewy bodies	
Kovari et al. [18]	2003	22 PD	Clinical dementia rating scale (CDR)+quantification of Lewy bodies, tangles and plaques in areas 9, 21, 24, 40 and entorhinal cx	CDR correlated with entorhinal and area 24 Lewy scores Entorhinal Lewy & plaque densities explained 36.2% and 19.3% of CDR variability, respectively	• Retrospective • α-synuclein immunostaining
Braak et al. [19]	2005	88 PD	MMSE, Braak stages for α-synuclein and tau pathologies	MMSE scores correlated with α-synuclein neuropathologic stages Higher neurofibrillary pathology stages and Aβ deposition in cognitively impaired cases	
Pletnikova et al. [20]	2005	21 PD+DLB	α-synuclein and Aβ immunohistochemistry and immunoblots	Few or no cortical Lewy bodies in brains without Aβ The opposite in brains with Aβ (specifically in the cingulate cortex)	
Aarsland et al. [21]	2005	22 PD	Aβ CERAD classification and Braak stages for α-synuclein and tau	18 developed PDD → none met AD neuropathological definition Cortical Lewy bodies were the main substrate of cognitive impairment	• Prospective
Ballard et al. [22]	2006	28 PDD+29 DLB	MMSE & UPDRS	Longer time from parkinsonism to dementia was associated with less severe cortical α-synuclein pathology and CERAD Aβ scores, but not Braak staging	• α-synuclein immunostaining
Haliday et al. [23]	2008	29 PDND+ 52 PDD+ 6 DLB		Cases with shorter survivals had more Lewy and plaque pathology	
Sabbagh et al. [24]	2009	28 PDD+AD 23 PDD-AD		PDD+AD subjects were older at onset and death, and progressed faster to dementia; about one half of cases met AD neuropathological criteria	
Jellinger & Attems [25]	2008	54 PDND+ 44 PDD+ 20 DLB	α-synuclein, tau & Aβ immunohistochemistry	Braak stages for α-synuclein & tau as well as cortical Aß plaque load, and generalized cerebral amyloid angiopathy or CAA) were significantly higher/more severe in DLB and PDD than in PD	

Table 1
Continued

Reference	*Year*	*Sample*	*Main outcomes*	*Main findings*	*Comments*
Lashley et al. [26]	2008	40 PD 20 controls	Semiquantitative Aβ plaques & CAA scores Morphometric approach for Lewy pathology	Aβ load correlated with cortical Lewy burden This correlation was more marked in cases with moderate to high Aβ load	• Retrospective
Kalaitzakis et al. [27]	2009	14 PDND 16 PDD	α-synuclein, tau, and Aβ deposition in the caudate, putamen, and accumbens	α-synuclein and tau deposition were rare in the striatum in both groups Aβ burden was greater in the striatum of PDD than in PDND	• α-synuclein immunostaining
Compta et al. [28]	2011	27 PDND 29 PDD	Braak stages for α-synuclein and tau	Cortical Aβ+cortical Lew scores+Braak tau stages in combination predicted better dementia than each separately	
			Semiquantitative Aβ plaques & CAA scores	Cortical Aβ scores & Braak tau stages, but not Lewy body scores or Braak α-synuclein stages, significantly correlated with MMSE scores	
			Lewy densities and semiquantitative scores	High cortical Aβ score and older age at onset were associated with a shorter time-to-dementia period.	
Irwin et al. [29]	2012	48 PDND 92 PDD	Semiquantitative scores for neurofibrillary tangles, Aβ plaques & Lewy bodies/neurites	Cortical Lewy scores+APOE4 were the stronger correlates of dementia PDD+AD cases were older, had more Lewy pathology and CAA	
Kotzbauer et al. [30]	2012	32 PDD	α-synuclein, tau & Aβ immunohistochemistry	Patients with synucleinopathy+Aβ had significantly shorter survival	
Sierra et al. [31]	2016	10 PD 10 PDD 10 DLB 10 AD 10 controls	Semiquantitative scores for α-synuclein, Aβ and neurofibrillary tangles in the midbrain (substantia nigra & tectum)+cerebellum (for Aβ)	α-synuclein midbrain scores rose from controls to AD and then LBD irrespective of dementia Aβ and tau more prominent in the tectum increasing from controls to LBD (mostly dementia cases) then peaking in AD Cerebellar Aβ scores were marginal in the LBD-spectrum (as opposed to AD) only showing a trend towards greater involvement in dementia cases	
Irwin et al. [32]	2017	213 LBD	Semiquantitative scores for neurofibrillary tangles, Aβ plaques & Lewy bodies/neurites	Greater Alzheimer pathology (chiefly of neurofibrillary type) implied higher α-synuclein scores and shorter time-to-dementia	

Aβ, amyloid-β; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; LBD, Lewy body disorder; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PDND, Parkinson's disease non-demented.

pathology in AD, since research on the so-called non-amyloid component of plaques (NACP) [33] started long before the identification of alpha-synuclein as the main constituent of Lewy bodies [13]. Subsequently, several studies have consistently shown that both in sporadic and in genetically determined AD (such as in *PSEN1* familial AD and in Down's syndrome) Lewy pathology is common, particularly in the amygdala, but also in the olfactory bulb, as summarized in Table 2 [34–38].

SUMMARY OF CO-PATHOLOGY IN PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE

The concurrence of Alzheimer and Lewy pathologies in structures such as the amygdala and the olfactory bulb, which are commonly affected in both conditions (i.e., PD and AD) is scientifically intriguing, and, as the aforementioned co-existence of Alzheimer and Lewy pathologies, is in keeping with the experimental evidence supportive of pathological synergism. Thus, these proteins have been shown being capable of cross seeding and promoting each other's aggregation [39], most probably not in all instances, but specifically when some protein strains are present [40]. While these experimental works are not free of criticism (mostly regarding as to what extent they can translate to what actually happens in humans and in disease), they provide a basis for further studies to understand how these proteins form disease-associated aggregates and, ultimately test specific anti-protein-aggregation agents. Discussion of such experimental studies is beyond the scope of this review and we refer to reviews published elsewhere [3].

NEUROPATHOLOGICAL EVIDENCE OF SYNAPTIC DYSFUNCTION IN PD AND AD

Synaptic dysfunction is a relatively new player in the field, since it is not as easily assessable as protein aggregation, for which immunohistochemistry provides a robust tool, albeit not devoid of limitations.

Lewy body disorders can be considered as a clinicopathological spectrum encompassing PD, PD-dementia (PDD) and dementia with Lewy bodies (DLB), rather than a group of truly distinct conditions. Across this spectrum, the use of non-conventional light microscopy techniques, has allowed for sensitive and selective detection of presynaptic α-synuclein aggregates and visualization and semi-quantitation of post-synaptic dendritic spines. For instance, in a study applying the paraffin-embedded tissue (PET) blot and the protein aggregate filtration (PAF) assay, Kramer and Schulz-Schaeffer observed with the PET blot a large amount of very small α-synuclein aggregates, which, using the PAF assay, were most frequently found in presynaptic terminals. This finding was mirrored by an almost complete loss of postsynaptic dendritic spines, in sharp contrast to the relatively small amount of cortical Lewy bodies, particularly compared to the severity of cognitive impairment seen in PDD and DLB [41]. Accordingly, these authors proposed presynaptic α-synuclein aggregates and the loss of dendritic spines as critical events for neurodegeneration in Lewy-related disorders [41, 42].

Also focusing on samples of DLB cases, Colom-Cadena and co-workers applied a microscopy technique called array tomography (which combines ultrathin tissue sections with immunofluorescence to visualize and quantify small structures such as the synapses) to assess presynaptic phosphorylated α-synuclein in the cingulate cortex and striatum from 5 DLB cases and compared them to 5 AD and 5 control cases. Hence, the authors found that 19% to 25% of phosphorylated α-synuclein aggregates were in presynaptic terminals with synaptic terminals co-localizing with these small aggregates being larger than terminals without such aggregates. There was also a gradient in the presence of phosphorylated synaptic α-synuclein aggregates, with their greater presence presynaptically suggesting a primary role for the presynaptic compartment [43].

Other authors have aimed at assessing other synaptic alterations such as suboptimal energy metabolism, and oxidative and endoplasmic reticulum stress damage in preclinical PD by means of studying incidental Lewy bodies [44]. Finally, it remains a matter of debate to what extent levodopa influences synaptic dysfunction in PD, as for decades many have made observations supportive of the notion that levodopa is harmful [45], whereas others have not [46].

Synaptic dysfunction is also considered in the pathophysiology of AD. In this vein, loss of dendritic spines has been correlated with loss of synaptic function [47–49]. Intriguingly, Aβ, both in its insoluble (fibrils and plaques) and its soluble (oligomers) forms, either extra or intracellularly, has been suggested to precede and lead to dysfunction of dendritic spines in experimental and pathological studies by a number of mechanisms ranging from reduced

Table 2
Summary of relevant neuropathological evidence of Lewy-type co-pathology in Alzheimer's disease

Reference	*Year*	*Sample*	*Main outcomes*	*Main findings*	*Comments*
Leverenz et al. [34]	1986	40 sporadic AD	Neuronal loss, Lewy bodies, or neurofibrillary tangles in the substantia nigra	18 patients had > 1 of these changes 13 of them had featured rigidity+/- tremor 9 had had a second diagnosis of PD 11 (85%) had PD pathologic changes	Pre-α-synuclein studies
Ditter et al. [35]	1987	20 sporadic AD	Lewy body formation, neuronal loss, and gliosis of pigmented nuclei Controlled for use of neuroleptic medication	11 cases (55%) showed PD changes No significant difference in age or symptom duration in AD+PD vs. AD-PD History of rigidity in 80% of AD+PD but only 14% of AD-PD Tremor not observed in either AD+PD or AD-PD	
Lippa et al. [4]	1998	74 cases of familial AD	Immunohistochemistry with antibodies to α/β/γ-synuclein	In at least in 22% of the entire cohort there were α-synuclein-immunoreactive Lewy bodies. In 12 of the 19 fAD cases (63%), in which the amygdala was investigated, Lewy bodies were found in this structure	First study investigating using α-synuclein immunohistochemistry in a large cohort of fAD
Lippa et al. [36]	1999	20 Down's syndrome	Immunohistochemistry with antibodies to α/β/γ-synuclein	Many α-synuclein+Lewy bodies and neurites in 50% of amygdala samples with Alzheimer pathology No positivity for β or γ synuclein	First study using α-synuclein immunohistochemistry in Down's syndrome cases with Alzheimer pathology
Hamilton et al. [4]	2000	145 sporadic AD	Immunohistochemistry with antibodies to α-synuclein	Lewy bodies found in 88/145 (60.7%) of CERAD cases and 56.8% of 95 cases with Braak stage 5-6) The amygdala was severely involved in all cases Absent to mild Lewy pathology in the substantia nigra	First large study using α-synuclein immunohistochemistry in late onset sporadic AD cases
Arai et al. [5]	2001	27 sporadic AD	Relationship between Alzheimer pathology and α-synuclein aggregation	13 of 27 cases (48.2%) had α-synuclein+structures including Lewy bodies Frequency and density of plaques and tangles did not differ between+and – cases α-synuclein+structures most frequent in the amygdala α-synuclein+structures different from Lewy bodies more frequent in the hippocampus Lewy-related structures even in AD cases with widespread and numerous tangles	No direct correlation between Alzheimer and Lewy lesions, but Lewy pathology present even in cases and locations with more severe tau degeneration (hippocampus)
Fujishiro et al. [37]	2008	41AD with amygdala Lewy bodies (AD-ALB) 21 AD without ALB	α-synuclein pathology in the olfactory bulb in AD with and without ALB	α-synuclein pathology detected in the olfactory bulb in 38/41 AD+ALB (93%) and 4 of 21 AD-ALB (19%) Double immunolabeling revealed co-localization of tau and α-synuclein in neurons and neurites of the olfactory bulb	Co-localization of tau and α-synuclein in the olfactory bulb
Savica et al. [38]	2019	32 DLB/AD, 54 ADLB, 70 AD, 41 PDD/AD cases		AD subjects with LTS pathology had higher UPDRS II and III total scores as well as generally higher individual scores compared to AD alone Depression scales and Trail-making Test A correlated significantly with LTS	Prospective design

AD, Alzheimer's disease; AD-ALB, Alzheimer's disease with amygdala Lewy bodies; ADLB, AD cases with LTS, but not meeting the criteria of DLB; DLB, dementia with Lewy bodies; fAD, familial Alzheimer's disease; LTS, Lewy-type synucleinopathy; PD, Parkinson's disease; PDD, Parkinson's disease dementia.

spine formation, stability and plasticity (inhibited long-term potentiation and enhanced long-term depression), to abnormalities in synaptic scaffold proteins and impaired organelle transport [50–56]. Tau hyperphosphorylation and microglia activation, which according to the amyloid cascade hypothesis are events secondary to Aβ pathology, appear to contribute to spine failure in AD as well [57]. Recently the postsynaptic protein neurogranin has been found to be reduced in brain tissue in AD [58].

Therefore, synaptic dysfunction in PD, DLB and AD, appears to be an attractive target both for improving knowledge of disease mechanism and developing new therapies, since preserved synaptic spines have been in turn linked to resilience against neurodegeneration [59]. Should the synaptic failure hypothesis hold true, it would theoretically be possible to revert it. However, unlike Aβ and tau pathologies, its assessment neuropathologically is not straightforward, since this requires the aforementioned sophisticated methodologies, whereas in terms of biomarkers (see next sections) it faces the controversy of whether it is already reflected by available biomarkers (such as Aβ, tau and α-synuclein) due to their close correlation, or it needs from more specific markers (as proper synaptic proteins). Thus, synaptic dysfunction to date remains investigational and awaits further studies, both neuropathologically and with biomarkers, particularly in terms of the similarities that synaptic dysfunction might have between PD and AD.

BIOMARKER EVIDENCE OF UNDERLYING PROTEINOPATHY AND SYNAPTIC DYSFUNCTION IN PD

One of the main aims of research in biomarkers in neurodegenerative disorders such as PD and AD is that they can make it possible to obtain information about the underlying neuropathology *in vivo* early in the disease process as opposed to traditional post-mortem neuropathological assessments, which most often provides information about end stage disease. There are several different types and sources of biomarkers for both PD and AD, but those that most directly reflect (or at least aim at reflecting) underlying pathology are CSF and positron emission tomography (PET) biomarkers.

In PD the obvious choice as either CSF or PET marker is α-synuclein. Over the last decade the number of studies on the levels of different α-synuclein species in CSF (mostly total and oligomeric) has rapidly increased, albeit with remarkable inconsistencies, most likely related to several pre-analytic and analytic factors. However, overall the trend is that CSF total α-synuclein levels are lowered in PD and other synucleinopathies vs. controls and other neurodegenerative conditions [60, 61], with the opposite occurring with CSF levels of oligomeric α-synuclein [62]. This notwithstanding, the interpretation of CSF markers appears to be more difficult in terms of PD-related cognitive impairment. Thus, few studies have found that CSF levels of oligomeric α-synuclein also tend to increase in PDD and DLB [63, 64] (that is, consistent with its trend as a diagnostic marker), but CSF total α-synuclein has shown conflicting results, with a number of cross-sectional and longitudinal studies having even suggested that high (instead of low) CSF total α-synuclein might be a correlate of cognitive impairment [64–66]. All these findings have led to speculations that low CSF total α-synuclein might be a diagnostic marker in the setting of either sequestration of α-synuclein within the intraneuronal aggregates, or a compensatory reuptake of the protein to maintain the synaptic homeostasis. Conversely, as disease progresses and there is greater neuronal damage and cell death, the levels would increase due to the leakage of the proteins from the intracellular space to the CSF. How this would relate to the CSF levels of the AD-related proteins (tau and Aβ) in PD is not straightforward. CSF total α-synuclein has been reported to correlate positively with both CSF Aβ and CSF tau levels [63, 66], but low CSF Aβ has been consistently associated with poor cognitive outcome [67–69], whereas CSF tau has been reported to be either normal or low [63] in early disease stages, but increased in a proportion of late stage PDD cases [70, 71]. Therefore, in PD low CSF Aβ levels, as in AD, might reflect sequestration of Aβ in extracellular parenchymal Aβ deposits (senile plaques), while CSF total α-synuclein would range from being low to increase paralleling what happens with CSF tau and reflecting increasing neuronal loss.

Alternatively, all these trends and correlations might be unrelated to aggregation and deposition of these proteins and their trafficking from the intra or extracellular space to CSF, and rather reflect other processes, as for instance synaptic dysfunction, as previously mentioned. Yet, this view would be challenged by PET marker studies, which are available and reasonably reliable for Aβ [72] and tau [73], but not yet for α-synuclein. Hence, to date published

data of studies on Aβ imaging in PD and DLB have ranged from negligible uptake in PD and moderately increased binding in DLB [74, 75] to more consistently showing a correlation of Aβ imaging and CSF Aβ levels longitudinally with cognitive outcome in PD [76, 77]. More recently, similar data emerged for tau in PD and DLB in two independent studies, albeit the tau PET uptake correlated with amyloid imaging only in one of the studies and not in the other [78, 79]. Therefore, if molecular imaging of Aβ and tau is showing anatomically that there are Aβ and tau lesions in the brains of PD and DLB patients and PET and CSF findings are significantly correlated, it is reasonable to presume that CSF and PET Aβ and tau markers are reflecting, at least partly, the underlying pathology. Few reports of autopsy findings in patients, having previously undergone CSF or PET studies, would also support this notion [68, 80, 81], but caution is still needed with tau imaging, as a recent autopsy report has shown the presence of off-target binding (neuromelanin, choroid plexus, haemorrhages) for the tau PET tracer 18F-AV-1451 [82].

In summary, to date the published CSF and PET studies are overall in keeping with the aforementioned neuropathological studies in that a remarkable proportion of PD patients have conjoint Lewy and Alzheimer pathologies, and that these clinically correlate with cognitive impairment.

This leaves open the question for specific markers of synaptic dysfunction in PD. In this area, the evidence is very limited, with the available information to date coming from proteomic approaches and hypothesis-driven studies [83–86]. Hence, in a CSF proteomic study synaptic markers, among other proteins, were detected to differ between different forms of atypical parkinsonism, PD and controls [83] and a subsequent meta-analysis of 27 proteomic studies, which found a total of 500 differentially expressed proteins, concluded that presynaptic proteins involved in vesicle membrane fusion such as SNAP25 could potentially be used as biomarkers for PD [84]. In this vein, a post-mortem study has found associations of cognitive decline in DLB and AD with Rab3 in the inferior parietal lobe and SNAP25 in the prefrontal cortex, respectively [85]. The same research group recently published a study of these proteins in CSF and found increased CSF levels of SNAP25 and neurogranin in relation to cognitive and motor symptom severity [86].

A summary of published sensitivities and specificities of α-synuclein markers is provided in Supplementary Table 1.

BIOMARKER EVIDENCE OF UNDERLYING PROTEINOPATHY AND SYNAPTIC DYSFUNCTION IN AD

In AD as in PD the accumulated evidence of biomarkers of α-synuclein pathology is indeed restricted to CSF studies, since, as already discussed there is not as yet any validated PET probe specific for α-synuclein. Studies available to date have also displayed discrepancies regarding CSF total α-synuclein. Thus, some studies have found no differences in CSF total α-synuclein between synucleinopathies (PD and DLB) and AD [87–89], whereas others have shown an association between low CSF total α-synuclein levels in AD and scores of a global cognition test such as the mini mental state examination test, suggesting that it constituted a general marker of synapse loss [8]. Yet, several published reports have pointed towards increased levels of CSF total α-synuclein in AD [90–93], linking it to aggressive neurodegeneration in this condition, in a similar way to high levels of CSF tau and 14-3-3 proteins in the setting of aggressive neuronal death as seen in Creutzfeldt-Jakob disease or AD itself.

Regarding CSF indicators of synaptic dysfunction in AD, besides the already discussed possibility that it can be captured by proteins that accumulate in PD and AD, synaptic proteins partly overlapping with those above referenced to PD have been assessed in AD as well, in fact before and more extensively than in PD. Hence, there are several studies which reported increased CSF levels of neurogranin [94–96], synaptotagmin [97], and contactin [98] in AD both in its clinically manifest phase and its prodromal stage as reflected by mild cognitive impairment with biological evidence of underlying AD (that is, CSF tau and Aβ abnormalities), suggesting these might be independent and complementary biomarkers of AD [99–101] Accordingly, a recent meta-analysis supports including neurogranin to the panel of AD biomarkers [102] Nevertheless, there are outstanding issues regarding specificity, since as happens with proteins such as tau, increased CSF levels neurogranin might merely reflect neuronal damage in aggressive conditions such as Creutzfeldt-Jakob disease [103].

As for synaptic CSF makers in PD, recently CSF levels of neurogranin have been assessed in parkinsonian disorders, with the finding that these were reduced in PD, PDD, MSA and PSP relative to AD and controls, not correlating with motor or cognitive measures, though [104]. By contrast, in another study

Table 3
Putative correspondence between neuropathological and biomarker similarities in Parkinson's disease and Alzheimer's disease

Neuropathology	*Biomarker finding*
Loss of pre and/or postsynaptic integrity, including dendritic spines	CSF levels of specific synaptic proteins (SNAP25, synaptotagmin, neurogranin)
Small protein aggregates with non-conventional approaches as PET blot, PAF assay or array tomography	CSF levels of α-synuclein or Aβ or phosphorylated tau
Larger protein aggregates by traditional immunohistochemistry	PET imaging of Aβ
Neuromelanin and other potential off-target binding structures to be considered	PET imaging of tau (PET imaging of α-synuclein when it becomes available?)

Aβ, amyloid-β; CSF, cerebrospinal fluid; PAF assay, protein aggregate filtration assay; PET blot, paraffin-embedded tissue blot; PET imaging, positron emission tomography imaging.

increased neurogranin CSF levels mirrored reduced CSF Aβ in PD and in this case a significant correlation with cognition (as measured by MMSE) was reported [105]. Hence more studies are needed to elucidate the actual associations of these synaptic markers in degenerative parkinsonian disorders.

Currently these markers are being explored not only in CSF, but also in blood exosomes, which would provide a more accessible source relative to CSF [106].

An overview of published sensitivities and specificities of τ and Aβ markers is summarized in Supplementary Table 1.

OTHER BIOMARKERS IN AD AND PD RESEARCH

Although it is not in the scope of this review, the increasing interest in neurofilaments and markers of neuroinflammation as biomarkers in both AD and PD, needs also to be mentioned. Neurofilament has been identified as a marker of disease progression or prognostic marker in several neurological conditions from multiple sclerosis [107] to amyotrophic lateral sclerosis [108] and, importantly also in both AD [109] and PD [110]. A major breakthrough in the research of this biomarker has been the demonstration that its levels in plasma significantly correlate with those in the CSF [111], making it a much more accessible biomarker. As for markers of neuroinflammation, there is research of both neuronal-specific (YKL-40 [112]) and non-specific markers (cytokines [113]) as diagnostic and progression biomarkers in AD and PD

CONCLUSIONS

There is compelling evidence that PD and AD share neuropathological hallmarks in that Aβ and tau lesions of the Alzheimer-type are common in PD and, vice versa, α-synuclein Lewy-type aggregates are frequent findings in AD. Modern non-conventional techniques overcoming limitations of routine immunohistochemical techniques are promising as to take further our knowledge of the impact of these disease-associated proteinaceous aggregates beyond the neurons' soma, down to their presynaptic and postsynaptic terminals, with potential mechanistic and even future therapeutic implications.

An even greater challenge is translating this knowledge to the clinic. CSF and PET markers of Aβ and tau work reasonably well in the AD field, but their counterparts in PD are far from being equally reliable, with new promising approaches being those of aggregometric techniques such as real time quaking induced conversion (RT-QuIC) [114]. In terms of PET markers, beside the fact that there is no PET probe available for α-synuclein yet, the AD PET markers range from consistent evidence of their specificity (amyloid imaging) to greater uncertainty of their reliability due to off-target binding (tau imaging). CSF synaptic markers are attractive, but evidence is still scarce and most probably these will be non-specific markers of disease progression. For all of these CSF and PET markers, one should remember that 'markers are not always makers', and therefore caution is needed when interpreting associations as causative.

In summary and coming back to the question raised in the title of this review (what are the relevant similarities between PD and AD? the protein aggregates? synaptic dysfunction? or both?), from a neuropathological point of view protein aggregates are there both at the soma and the synapse. Thus, a number of CSF and PET biomarkers might capture these different faces of protein-related neurodegeneration. More specifically, CSF α-synuclein, tau and Aβ levels might reflect beside underlying protein aggregates also the soluble fractions of these proteins at the synapse level (Table 3).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

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