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REVIEW

The morbid anatomy of dementia in Parkinson's disease

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Abstract Dementia in Parkinson's disease (PD/PDD) is a common complication with a prevalence of up to 50%, but the specific changes underlying the cognitive decline remain undefined. Neuronal degeneration resulting in the dysfunction of multiple subcortical neurochemical projection systems has been described along with Lewy body-type pathology in cortical and limbic regions. Advanced alpha-synuclein (αSyn) pathology is not necessarily sufficient for producing dementia and concomitant Alzheimer's disease (AD) change has also been proposed as a possible substrate of PDD. A lack of consensus in the extant literature likely stems from clinical heterogeneity and variable reliability in clinical characterisation as well as other historical and methodological issues. The concurrent presence of abnormally deposited αSyn, amyloid-β and tau proteins in the PDD brain and the interaction of these molecules in a linked pathological cascade of AD and PD-related mechanisms may prove important in determining the underlying pathological process for the development of dementia in PD and this concept of combined pathologies awaits further investigation.

Keywords Parkinson's disease · Alpha-synuclein · Lewy body · Neuropathology · Dementia · Cognitive dysfunction · Beta-amyloid · Tau

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Introduction

In 1817, James Parkinson in his classic treatise "An Essay on the Shaking Palsy" cogently described many of the salient motor features of the disorder but also stated "…the senses and intellects being uninjured". Today, however, Parkinson's disease (PD) is viewed as a neurodegenerative condition characterised clinically by a variety of non-motor complications including neuropsychiatric and autonomic/vegetative features in addition to the core motor syndrome. Although the classical motor signs in PD are ascribed in the main to dopaminergic cell loss in the substantia nigra pars compacta [43] resulting in striatal dopamine depletion, the anatomical and pathological substrate underlying dementia has been a matter of controversy. Dementia is highly prevalent in PD and predicts an increased risk for nursing home placement [4], more rapid disease progression [123], greater caregiver burden, reduced patient and caregiver quality of life [3] and increased mortality [90, 92].

In this report, we review the literature concerning the anatomical and pathological substrates underlying dementia and cognitive dysfunction in PD.

Epidemiology

The prevalence of PD is about 1% of those aged 60 years and over and increases with age [36]. The mean age at disease onset is in the early to mid-60s [65]. Life expectancy in Western countries has increased over the last several decades [114] and PD patients share the gain in longevity with the life span of contemporary patients longer than that of 30 or 50 years ago and not significantly lower than the average life expectancy.

The epidemiology of PD with dementia (PDD) is difficult to evaluate accurately due to differences in patient populations, study design and criteria for diagnosing PDD. Amongst all cases of dementia, studies have estimated that 3–4% are due to PDD [35]. Cross-sectional studies in PD cohorts, providing point prevalence estimates of dementia, have yielded frequencies between 10 and 40% [6, 29, 102]. Prospective studies have reported a cumulative incidence of 19–53% [62]. When compared with the age-matched healthy control subjects, the risk for developing dementia in PD patients increases up to six-fold [2]. Because mortality is higher amongst demented subjects, period (or cumulative) prevalence estimates provide a more reliable picture of the presence of dementia in PD [42]. The cumulative prevalence of dementia in PD has been reported to range between 48 and 78% [1, 56] and in patients surviving for 20 years or longer with the illness, as is increasingly common, the vast majority will develop dementia or serious cognitive difficulties [26].

Although cognitive symptoms usually occur at later stages of the disease, a few studies have reported cognitive deficits at the time of diagnosis of PD. Muslimovic et al. [106] found 24% of patients with newly diagnosed PD showing cognitive impairment, whilst in another study by Foltynie et al. [44] 36% of patients amongst 239 newly diagnosed PD patients had similar findings. Thus, even at the time of diagnosis, cognitive decline can be identified in a significant number of PD patients.

There are a number of features that consistently associate with dementia in PD including advanced age at onset, a longer duration of disease, an akinetic rigid syndrome with symmetrical signs, impairment of gait and balance, higher disability and bradykinesia scores [41, 57, 101, 115], major depression or depressive symptoms and other unusual or atypical neurological features such as the early occurrence of autonomic failure, and a poor to moderate response to dopaminergic treatment [6, 8, 42, 58].

Although it is well established that the apolipoprotein E (ApoE) 4 allele confers an increased risk for Alzheimer's disease (AD), studies examining this gene and susceptibility to dementia in PD have produced contradictory findings, with reports failing to predict a higher risk for dementia [64, 134] contrasting with others implicating a higher prevalence of dementia in PD with the ApoE 4 allele [60, 110]. It is important to note that meta-analysis reviews examining the impact of the ApoE 4 allele on dementia in PD may reflect the inclusion of studies not using uniform diagnostic criteria for dementia in PD along with pathological confirmation.

Clinical features of dementia in PD

Dementia involves the impairment of multiple domains of cognition. Since the mid-1970s, one view has been that dementia can be separated into cortical and subcortical types, a distinction that has found support from both clinical [111] as well as pathological perspectives [34]. Individuals with Parkinsonism are most often elderly and may harbour multiple cerebral pathologies contributing both to motor deficits and cognitive decline yielding a heterogeneous clinical picture. Our discussion relates to the well-recognised disorder of Lewy body PD complicated by progressive cognitive decline culminating in dementia without significant co-morbidities such as AD, significant cerebrovascular disease or other remarkable brain pathology. The dementia syndrome in PD has been extensively studied. Recently, the movement disorder society recruited a task force to define the clinical diagnostic criteria for PDD [42]. According to this diagnostic criteria abnormalities of attention, concentration, memory, word list generation, abstraction and categorisation, judgement, problem resolution, strategy formulation and visuospatial dysfunction (such as problems with visual discrimination, visual organisation, spatial orientation, drawing and angle perception) represent core features of the dementia syndrome in PD [50, 89]. In addition to intellectual/cognitive impairment, hallucinations, delusions, apathy, excessive daytime sleepiness and abnormalities of mood and personality change including, depression, mania and psychosis have also been described in PDD [31, 42]. The neurobehavioural and neuropsychiatric clinical profile of dementia in PD occurs in the absence of prominent apraxia, aphasia and agnosia, clinical features that are more typically characteristic of 'cortical' dementias such as AD.

Neuropathology of dementia in PD

α-Synucleinopathy

The classical neuropathological feature of PD is the presence of neuronal intracytoplasmic inclusions known as LBs and inclusions confined to neuronal processes known as Lewy neurites (LN). The discovery that α-synuclein (αSyn) gene mutations can cause PD [88, 113] and that the encoded protein constitutes a major component of LB and LN [122] has provided the basis for a molecular definition of the disease and a better understanding of its pathogenesis. In fact, the term 'synucleinopathy' has been used to designate a spectrum of degenerative diseases that share the presence of abnormal αSyn immunoreactive inclusion

bodies in neurons and/or glial cells [46, 127] with the term encompassing diverse, but clinically overlapping entities, such as multiple system atrophy, PD, dementia with Lewy bodies (DLB), the LB variant of Alzheimer's disease (LBVAD) and neurodegeneration with brain iron accumulation type 1 (NBIA I) [9, 13, 38, 45, 107].

PD is the most frequently occurring synucleinopathy. The involvement of the substantia nigra with the destruction of dopaminergic neurons in the pars compacta is the universally acknowledged hallmark of PD [33, 95]. However, PD is a 'multisystem' illness with pathology occurring in a variety of cortical and subcortical regions including, but not limited to: the olfactory bulb and related areas, the spinal cord, the dorsal motor nucleus of the vagus nerve, the pedunculopontine nucleus, non-thalamic nuclear nuclei with diffuse projections to cortical and subcortical regions, intralaminar and midline thalamic nuclei, the amygdala, nucleus basalis of Meynert (NBM), transentorhinal cortex, hippocampal formation, temporal and frontal cortices as well as autonomic nerves (e.g. cardiac and abdominopelvic autonomic plexuses) [20, 23, 67, 72, 80, 82, 83, 105, 116, 119].

Controversy over the underlying bases of dementia in PD

The widespread, yet selective, pathology observed in the PD brain accounts for the variety of non-motor symptoms seen in PD including dementia. Nevertheless, there is a debate in the literature regarding the particular changes underlying dementia in PD with no consensus as to whether dementia relates to LB disease-type pathology or rather concomitant AD-type changes or even a combination of both. In addition, the contributions of small vessel subcortical disease along with cortical vascular pathology have likely not received sufficient attention as aggravating factors in reducing cognitive reserve. Reasons for ongoing controversy include clinical heterogeneity in the cases studied with an obvious problem, especially in earlier studies residing in the inclusion of cases with dementia as a presenting feature. The temporal relationship between the clinical onset of parkinsonism and dementia currently defines two distinct clinical entities (PDD and DLB): if extrapyramidal symptoms precede dementia by more than 12 months the patient is classified as having PDD and if dementia and extrapyramidal symptoms develop together within a 12-month period or dementia precedes extrapyramidal symptoms then the patient is classified as having DLB [104]. Exceptions for the temporal relationship between the clinical onset of parkinsonism and dementia have also been described [76].

Difficulty in defining the underlying substrate of dementia in PD (and DLB) also relates to historical methodological/technical issues. LB were initially identified with the use of conventional histological techniques such as haematoxylin and eosin (H&E) staining that underestimates the presence of LB, especially in cortical regions. In the late 1980s immunohistochemistry (IHC) was introduced revealing the presence of a variety of antigenic components within LB. The most consistently recognised proteins were the cytoskeletal proteins neurofilaments (NFs) and ubiquitin (Ub) [51, 93]. Comparison of antibodies raised against NFs and Ub demonstrated that Ub-IHC was a more reliable and sensitive method for the detection of LB because antibodies against NFs only immunolabeled around half of the H&E-stained LB [32]. The use of Ub-IHC was especially helpful in detecting cortical LB that possesses a less conspicuous morphology than their brainstem counterparts. Nevertheless, it soon became apparent that Ub immunoreactivity was not unique to LB, but appears with other inclusions such as neurofibrillary tangles (NFTs) that were difficult to distinguish from LB [93]. αSyn IHC, introduced in 1997 [121, 122], has become the 'gold standard' for the detection of LB as it is a much more sensitive and specific technique and enables the distinction of LB from other pathological inclusions. Similarly, early descriptions of the AD histopathological features were based on the silver stains, amyloid stains and modifications thereof such as thioflavin-*S* fluorescence, Bielschowsky silver stain, Campbell–Switzer silver stain, Bodian stain and the Gallyas silver stain [37]. Although some of these stains (e.g. thioflavin-*S* fluorescence) are useful for the study of AD, they are not selective for a particular AD neuropathological feature. For instance, Bielschowsky silver stain detects both plaques and NFTs, whereas Campbell–Switzer silver stain and thioflavin-*S* fluorescence detect plaques, NFTs as well as LB [19, 103]. Immunohistochemical detection of AD-type pathology has proved superior to earlier stains as it is specific and sensitive to particular pathological features (i.e. plaques or NFTs) and provides a biologically meaningful stain that is derived from molecular and biochemical characteristics of the pathological change under study. In view of the methodological limitations of earlier studies, the current lack of consensus in defining the pathological changes producing dementia in PD is not surprising. Also, apart from the presence of classical inclusions, neuronal loss and comorbid vascular disease, the contribution of other less well-studied pathological changes, including glial involvement and impairment of neuronal (and axonal) function in the absence of morphological change on routine staining (e.g. loss of trophic factor and neurotransmitter enzymatic expression), must also be considered [130].

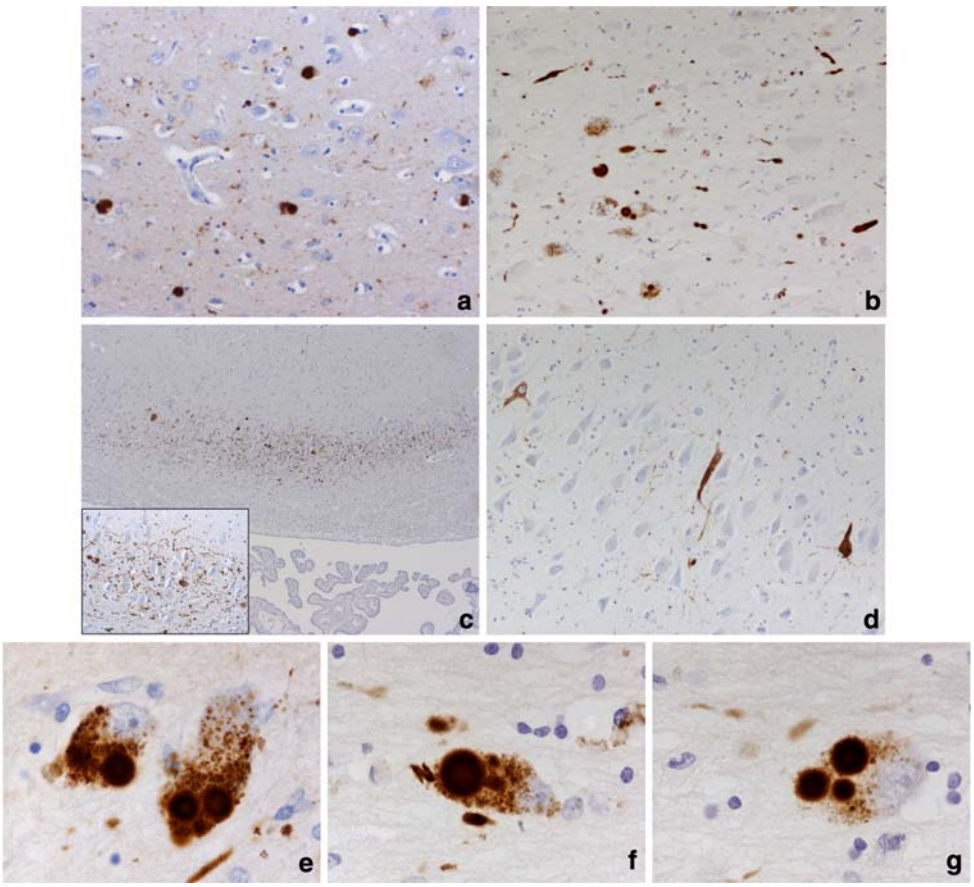

Fig. 1 Pathology in cortical and subcortical regions. **a** Cortical LB pathology in the cingulate gyrus of a demented PD case. **b** LB and LN pathology in the NBM of a demented PD case. **c** Selective vulnerability of the CA2 sector of the hippocampus to LN-type pathology. *Inset* higher magnification showing the web of LNs. **d** Neurofibrillary pathology in the CA2 sector of the hippocampus of a demented PD case. **e** Multiple 'classical' LB in a pigmented neuron of the medial substantia nigra. A single LB in a pigmented neuron is also evident. A single (**f**) and multiple (**g**) LB in a neuron of the NBM magnification: **a** and **b** ×20, **c** ×4 and for *inset* ×10 and **d** ×20, **e**, **f** and **g** ×100. *PD* Parkinson's disease, *LB* Lewy bodies, *LN* Lewy neurites, *NBM* nucleus basalis of Meynert, *CA Cornu Ammonis*

Degeneration of subcortical nuclei/neurochemical deficits and synaptic loss

In the PDD, brain degeneration of subcortical nuclei resulting in multiple neurochemical deficits is a well-established neuropathological finding and one of the earliest studies to report significant subcortical degeneration in demented versus non-demented PD cases was that of Gaspar and Gray [47], with neuronal loss in the locus coeruleus (LC) and in the nucleus basalis of Meynert (NBM) significantly more pronounced in demented cases. In addition, the same study reported LB in the NBM (95% of the cases) and a reduction in choline acetyltransferase activity in both the NBM and cortex. Yoshimura [135] as well as Kosaka et al. [86] and Sudarsky et al. [124] have all reported significant neuronal loss in the LC and NBM in demented PD cases independently of significant concomitant AD pathology. In PD, NBM cell loss averages 30–40% and is much higher in demented than non-demented PD patients [67]. However, severe cell loss in the NBM without overt dementia has also been reported suggesting that the degeneration of the NBM may precede the onset of mental dysfunction, with a critical threshold of neuronal loss along with equivalent cortical cholinergic denervation occurring before dementia becomes apparent [68]. We have also observed that the extent of αSyn pathology in the NBM is high in both demented and cognitively intact cases, highlighting a universal cholinergic deficit in PD with or without clinically evident cognitive decline [80] (Fig. 1b, f, g). The LC, the main source of noradrenergic input to the forebrain and neocortex, demonstrates neuronal loss that ranges from 40 to 50% and cell loss is more severe in demented PD subjects or those with depression than non-demented or non-depressed patients [69]. As a result of LC neuronal depletion, there is a reduced noradrenergic innervation of the forebrain and neocortex and apart from dementia and depression this may also relate to autonomic dysfunction [59]. The LC in PD shows not only cell loss, but also cell shrinkage that is independent of cortical pathological changes suggesting a primary degeneration of this nucleus [59].

The dorsal raphe nucleus (DRN) that gives rise to ascending serotonergic pathways also degenerates leading to a reduction in serotonin, its metabolites and receptors in the striatum and medial frontal cortex [7] with cell depletion averaging between 20 and 40% [67]. DRN cell loss is more severe in depressed than non-depressed patients and serotonergic deficiency has also been related to both cognitive dysfunction and dementia [7, 67, 75].

In PD, there is also a considerable loss of neurons in the ventral tegmental area (VTA), providing the major

dopaminergic input to meso-limbic and prefrontal areas. Dementia in PD patients has been associated with greater cell depletion in VTA (in the range of 40–60%) than in non-demented patients [137] and the contiguous medial substantia nigra has also been implicated as a substrate for dementia in PD (Fig. 1e) with Rinne et al. [117] reporting that the degree of dementia significantly correlates with the neuronal loss in the medial nigra, independently of concurrent AD pathology, leading the authors to suggest that intact projections to the caudate nucleus, limbic and cortical areas are essential for normal cognitive function. Whilst Jellinger and Paulus [75] have also reported that demented PD subjects demonstrate more cell loss in the medial nigra, this was accompanied by significantly more severe Alzheimer lesions in isocortex and hippocampus than in non-demented subjects.

Overall, these studies indicate that dementia in PD relates to subcortical neuronal degeneration and resultant neurochemical dysfunction of noradrenergic, serotonergic, dopaminergic and cholinergic projection systems and is not always associated with coincidental Alzheimer-type lesions.

In AD, synaptic integrity has been studied using synaptophysin, a 38-kDa integral membrane protein of synaptic vesicles. These studies have demonstrated a strong inverse correlation between levels of synaptophysin and dementia severity as measured by neuropsychological testing [126]. Synaptophysin levels also inversely correlate with indices of NFTs [17, 24]. The loss of synapses in DLB does not correlate as clearly with cognitive status. In studies of DLB, loss of synapses (measured by decreased levels of synaptophysin) has been demonstrated in the entorhinal cortex [133], yet, others using similar methods found no significant decrease in synaptophysin in the frontal cortex [120]. Synaptic loss and its contribution to the development of dementia in PD by and large has not been extensively studied. A study by Zhan et al. [136] found a reduction in synaptophysin in the pyramidal layer of the neocortex in both PD and PDD subjects, with the latter showing a greater loss of synapses compared with control cases. The authors conclude that the loss of synapses in the cortical neuropil may be a significant factor for the development of dementia. Further studies are warranted to investigate the contribution of synaptic loss to the development of dementia in PD as well as its relationship to αSyn, Aβ and tau deposition.

LB and αSyn

Since αSyn was recognised as the main component of LB, many studies have explored the relationship between LB burden and/or αSyn deposition and the presence/or severity of dementia in PD. With some important exceptions, these studies point to limbic and cortical LB pathology as the main determinant of the presence of dementia in PD. Mattila et al. examined the contribution of both PD and AD pathological lesions to dementia in PD and whilst demonstrating a strong association between LB in the frontal cortex and dementia and correlating NFTs in the entorhinal cortex and hippocampal CA1 area with cognitive impairment, using multivariate statistical analysis the authors found that cortical LB alone contribute to the severity of cognitive impairment, independently of concomitant AD pathology [98], results consistent with a previous study [100] by the same research group in which anti-ubiquitin immunostaining was used to identify cortical LB. Similar results have been reported by Hurtig et al., where cortical LB were found to be a more sensitive and specific correlate of dementia than AD-type pathology in 22 demented as compared to 20 non-demented PD subjects [63]. In another study, dementia correlated with LB densities in the entorhinal cortex and anterior cingulate gyrus [87]. In a study by Harding and Halliday [55] cortical LB densities did not separate cases of DLB from those with PDD although semiquantitative thresholds in the parahippocampus could separate demented from non-demented cases with high sensitivity and specificity. We have demonstrated that dementia in PD positively correlates with both αSyn deposition in a variety of cortical and subcortical structures as well as with AD (tau and Aβ) pathology [80]. Specifically, we have reported a significantly positive association of dementia in PD with αSyn in the anterior cingulate gyrus, superior frontal gyrus, temporal cortex, entorhinal cortex, amygdaloid complex and CA2 sector of the hippocampus (Fig. 1a, c). The relationship between αSyn burden in the anterior cingulate gyrus and dementia was so reliable that statistical analysis demonstrated that αSyn deposition in the anterior cingulate gyrus could differentiate cases with dementia from those without with high sensitivity and specificity (75 and 85%, respectively). This finding supports a primary role of αSyn in the pathological processes of cognitive dysfunction in PD as well as pointing to the anterior cingulate gyrus as an important focus of damage in PD. We have also recently demonstrated that αSyn and Aβ pathology in the claustrum, a region of largely obscure physiological function, strongly relates to the presence of dementia in PD and DLB [85].

Although most clinicopathological studies of dementia in PD are retrospective, a recent prospective community-based study conducted by Aarsland et al. [5] also indicated that LB pathology and not AD histopathological changes drive the progression of cognitive impairment in PD. This group showed that the LB score but not Braak and Braak stage, CERAD score, or chronic vascular lesions, was significantly associated with annual decline on Mini-Mental State Examination (MMSE) in a univariate

regression analyses. The authors conclude that 'Lewy body disease' is the main substrate driving the progression of cognitive impairment in PD.

Others have suggested LN-type pathology in the hippocampus as relating to cognitive decline and dementia in PD [15, 16, 27, 80]. More specifically, Churchyard and Lees [99] found a positive correlation between LN burden in the CA2 sector of the hippocampus and severity of dementia, although this correlation has remained controversial because ubiquitin IHC was used which is a less sensitive method for the visualisation of LB and LN pathology. Nevertheless, using αSyn IHC, we have confirmed numerous LN in the CA2 sector of the hippocampus as well as an association between LN in the CA2 sector of the hippocampus with dementia in PD [80] (Fig. 1c) indicating a role of this anatomical region in PDD.

Contesting these studies, others have found that a severe LB burden does not necessarily predict dementia or cognitive decline in PD. Colosimo et al. [28] demonstrated classic DLB pathology in PD patients without dementia and Parkkinen et al. [108] have also questioned the involvement of LB pathology in cortical and limbic structures in the development of dementia in PD.

In 2003, Braak et al. [21] devised a staging system according to which αSyn pathology progresses in a systematic fashion and proposed six distinct stages of PD. According to this design, the earliest pathology is to be observed in the DMV and olfactory bulb (stage 1) from where αSyn pathology is thought to proceed in a rostral direction via the pons (stage 2) to the midbrain (stage 3), and from there to the basal forebrain and mesocortex (stage 4) and finally spreading to/involving the neocortex (stages 5–6).

In a later study by the same group [22], an attempt was made to establish a link between cognitive status and the proposed PD stages. A decrease in the median MMSE scores between PD stages 3–6 was found suggesting that the risk of developing dementia increases with the disease progression. Statistical analysis demonstrated a strong positive correlation between the cognitive status of the individual patient and the neuropathological stage and this correlation was characterised by a linear trend.

Aside from several methodological shortcomings of the proposed PD staging system [81, 83, 84], its clinical relevance has also been questioned [25, 70, 71]. Parkkinen et al. [109] examined 226 αSyn-positive individuals and found that 55% of the cases corresponding to Braak's stages 5–6 lacked clinical signs of dementia or extrapyramidal signs. Given the retrospective nature of the Parkkinen et al. study, it is possible that a proportion of the 55% of cases described had motor and cognitive impairments that were not recorded, but even admitting this caveat, a majority of cases with Braak stages 5–6 would be expected to show obvious clinical signs (i.e. manifest Parkinsonism and cognitive impairment). Parkkinen et al. also demonstrate another weakness of the Braak staging system in that there is no firm requirement for minimum neocortical LB densities to be awarded a neocortical stage.

More recently in an attempt to address the limitations of previous staging systems Beach et al. [14] proposed a new staging system for αSyn with the so-called 'Unified staging system for Lewy body disorders'. According to Beach et al. subjects with Lewy-type α-synucleinopathy are classified into one of the following stages: I olfactory bulb only; IIa brainstem predominant; IIb limbic predominant; III brainstem and limbic; and IV neocortical. The authors found that progression through these stages is accompanied by a stepwise decline in striatal tyrosine hydroxylase concentration, substantia nigra pigmented neuron loss score, MMSE and Unified Parkinson's disease Rating Scale (UPDRS) part 3 scores.

AD pathology

AD pathology is commonly found in the PDD brain and clinicopathological studies have also pointed to AD-type pathology as an important determinant of dementia in PD. Hakim and Mathieson [54] examined 34 cases with PD, of which 19 had dementia and demonstrated an increased incidence of AD pathology. Boller et al. [18] and Jellinger and Grisold [66] also suggested AD-type pathology as the main cause of dementia in PD. Hughes et al. [61] found that amongst 100 PD cases examined, 44% had dementia; 29% had AD pathology, 10% had numerous cortical LB and only 6% had a possible vascular cause. Jellinger [68], in a large retrospective pathological study comprising 610 cases, attributed dementia to AD pathology, with only 3.5% of cases with 'pure' PD having dementia. Emphasis on AD-type pathology as the main substrate of dementia in PD has also been addressed in studies following the application of αSyn IHC. Jellinger et al. [77] examined the impact of coexisting AD pathology on the natural history of PD. They reported that dementia in PD significantly correlates with coexistent neuritic Alzheimer pathology, particularly when using the CERAD and NIA-R criteria for the diagnosis of AD. Although cerebral amyloid angiopathy (CAA) is not generally thought to relate to dementia or cognitive impairment in PD, a recent study by Jellinger and Attems [74] demonstrated that CAA was more severe in DLB and PDD cases than in subjects with PD without dementia.

Others have not found a strong association between AD pathology and dementia. Mastaglia et al. [97] using Aβ IHC found that dementia in PD is only infrequently due to fully established AD and Jendroska et al. [78] in an earlier study, also reported that dementia cannot be well explained

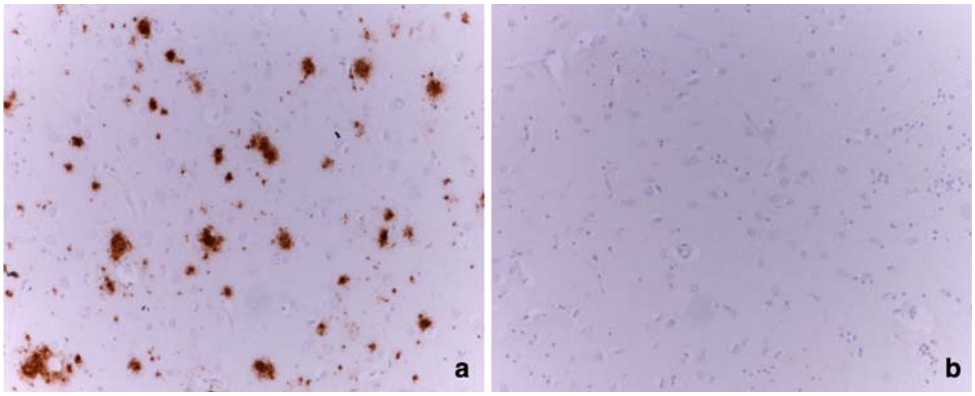

Fig. 2 Immunostaining for β-amyloid deposits in the caudate nucleus. **a** A large number of Aβ deposits in the caudate nucleus of a PD case with dementia. **b** Caudate nucleus without Aβ deposits from a non-demented PD case. Magnification ×20. *PD* Parkinson's disease, *Aβ* amyloid β peptide

by AD histopathological changes. We have observed a strong positive correlation between the presence of dementia and Aβ deposition in the anterior cingulate gyrus, entorhinal cortex, amygdaloid complex and nucleus basalis of Meynert as well as neurofibrillary changes in the CA2 sector of the hippocampus [80] (Fig. 1d), but αSyn pathology and not AD changes differentiated demented from non-demented PD cases with both high sensitivity and specificity.

Although several studies indicate cortical AD pathology as an important determinant for the development of dementia in PD, the significance of cortical plaques in AD and PD is questionable [10, 11, 87, 98, 128]. For example, there have been inconsistent reports on the correlation between cortical Aβ burden and various measures of clinical deficit in both diseases [132]. In addition, 'senile' plaques are found in the neocortex of elderly subjects without overt dementia and are viewed as part of normal ageing [12]. Recently, an increased awareness of striatal pathology in LB diseases has emerged with Duda et al. showing extensive αSyn pathology in the striatum [39]. The greatest density was found in patients with a combination of AD and DLB followed by cases with DLB alone. PD patients also showed mild to moderate changes. Similar findings have been reported by Tsuboi et al. [131]. Furthermore, Liang et al. [91] have shown abundant Aβ pathology in the striatum of cases with DLB that was more pronounced than in cases with PDD. Jellinger and Attems [73] have confirmed these findings in a larger cohort pointing to a morphological distinction between DLB and PDD on the basis of differing striatal pathology. In contrast to a debatable implication of cortical Aβ deposition, in a recent clinicopathological study, we have found Aβ deposition to be significantly greater in the striatum of PDD cases than in non-demented PD cases [82] (Fig. 2). In addition, striatal Aβ deposition was independent of AD changes in the cortex and was minimal in non-demented PD cases. This finding is of particular interest for several reasons. In contrast to cortical Aβ deposition, Aβ deposition in the striatum is universally found in AD brains, but is rarely observed in non-demented elderly individuals [48, 125]. Furthermore, according to phases of β-amyloidosis in the human brain proposed by Thal et al. [129], Aβ deposition in the striatum occurs in phase 3 with associated clinical dementia and, thus, appears to reflect a disease severity-specific pathological change in AD subjects. This evidence points to the striatum as an important anatomical region related to clinically overt dementia in AD. The finding that PDD cases also exhibit a significantly greater Aβ burden in the striatum as opposed to non-demented PD individuals not only makes the striatum a distinctive subcortical region in the development of dementia in PD, but also shows that Aβ striatal pathology strongly associates with clinical dementia. Imaging studies using Aβ ligands also report an increased Aβ burden in the striatum of cases with dementia [118], however, more recent PiB/PET studies have demonstrated minimal cortical or striatal PiB retention in PDD patients, whereas DLB patients show high levels of both cortical and striatal PiB retention, similar to the high levels found in AD patients [40, 52, 94]. Although our finding of high levels of striatal Aβ in PDD individuals contradicts these PiB/PET imaging studies, it is possible that Aβ deposits are present in the striatum in PDD but are not detected by PiB/PET imaging due to PiB having a lower affinity for diffuse Aβ deposits, such as those described in the striatum, compared with the aggregated form of Aβ found in cortical plaques of AD and DLB patients. Because PiB is also able to bind other cross β-structured proteins, such as αSyn more research into PiB–protein interactions is required to draw firm conclusions on the findings of PiB/PET imaging studies in PD and related disorders.

Molecular interaction of αSyn, tau and Aβ proteins

At least 70% of dementias in the elderly are related to abnormalities of αSyn, tau and Aβ proteins and this figure

increases to more than 90% for dementias of neurodegenerative origin [30]. It has become apparent that there is a strong interaction between αSyn, tau and Aβ at a molecular level. In vitro studies have shown αSyn binding to tau and inducing its phosphorylation [79]. αSyn induces fibrillisation of tau and coincubation of tau and αSyn synergistically promote mutual fibrillisation [49]. In vivo evidence of an interaction between αSyn and tau has also been reported with mice overexpressing human A53T *SNCA* demonstrating inclusions positive for αSyn as well as for tau [49]. Similarly, a link between Aβ and αSyn has been described with in vitro experiments showing Aβ42 promoting the formation of αSyn oligomers and polymers [96]. Cells transfected with *SNCA* and treated with Aβ42 form more inclusions than in the absence of Aβ42 [96]. Pletnikova et al. found that Aβ deposits in the cerebral cortex in PDD were associated with extensive αSyn lesions and higher levels of insoluble αSyn [112]. Therefore, Aβ peptides may contribute to an aggravation of LB pathology by promoting an aggregation of αSyn and exacerbating αSyn-dependent neuronal pathologies. An interaction between Aβ and tau has also been demonstrated with injection of β-amyloid Aβ42 fibrils into the brains of P301L mutant tau transgenic mice causing a fivefold increase in the number of NFTs in cell bodies [53] supporting the view that Aβ42 fibrils can accelerate NFTs formation in vivo. Given that in the PDD brain these proteins will co-exist to a varying degree, the identification for a specific primary pathological substrate for dementia in PD remains difficult. Further studies are needed to examine the interactions and impact of the coexistence of these pathogenic proteins in producing dementia in PD.

Coda

Dementia has a major impact on the natural history and prognosis of PD. The putative brain changes underlying dementia in PD have not yet been explored in sufficient detail to permit a consensus definition. Although some studies indicate LB-type pathology in cortical and limbic structures as the main histological substrate of PDD, it now appears that even widespread αSyn lesions often cannot reliably account for the presence of dementia with frequently encountered concomitant AD-type changes suggesting a synergism of multiple pathogenic molecules that requires future investigation. Further work from valid retrospective as well as prospective clinicopathological studies embracing the multiple implied pathologies underlying dementia in PD will provide novel mechanism-based treatments, with the potential to prevent, delay or arrest the development of cognitive impairment in PD.

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