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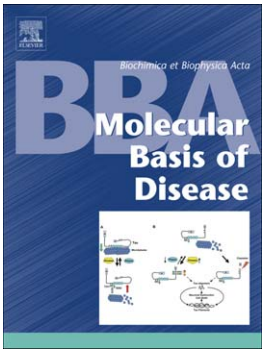

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Summary

The two most frequent synucleinopathies, Parkinson disease (PD) or brainstem predominant type of Lewy body disease, and dementia with Lewy bodies (DLB), are neurodegenerative multisystem disorders with widespread occurrence of a-synuclein containing deposits in the central and peripheral autonomic systems. For both Lewy body-related disorders staging/classification systems based on semiquantitative assessment of the distribution and progression pattern of a-synuclein pathology are used that are considered to be linked to clinical dysfunctions. In PD a six-stage system is suggested to indicate a predictable sequence of lesions with ascending progression from medullary and olfactory nuclei to the cortex, the first two presymptomatic stages related to incidental Lewy body disease, stages 3 and 4 presenting with motor symptoms and the last two (cortical) stages frequently associated with cognitive impairment. DLB, according to consensus pathologic guidelines, by semiquantitative scoring of a-synuclein pathology (Lewy body density and distribution) in specific brain regions, is distinguished into three phenotypes (brainstem, transitory/limbic and diffuse cortical), also considering concomitant Alzheimer-related pathology. Recent retrospective clinico-pathologic studies, although largely confirming the staging system, particularly for younger onset PD with long duration, have shown that between 6.3 and 43% of cases did not follow the proposed caudo-rostral progression pattern of a-synuclein pathology. In 7 to 8.3% of clinically manifested PD cases with synuclein inclusions in midbrain and cortex corresponding to LB stages 4-5 the medullary nuclei were spared, whereas mild parkinsonian symptoms were already observed in stages 2 and 3. There is considerable clinical and pathologic overlap between PD (with or without dementia) and DLB, corresponding to Braak LB stages 5 and 6, both frequently associated with variable Alzheimer-type pathology. Dementia often does not correlate with progressed stages of Lewy body pathology, but often is related to concomitant Alzheimer lesions or mixed pathologies. The relation between cortical Lewy body lesions and cognitive impairment is under discussion. On the other hand, in large unselected autopsy series 30 to 55% of elderly subjects with widespread a-synuclein pathology (Braak stages 5-6) revealed no definite neuropsychiatric symptoms or were not classifiable, indicating compensatory mechanisms of the brain. The causes and molecular basis of rather frequent deviations from the proposed caudo-rostral progression of a-synuclein pathology in PD, its relation to the onset of classical parkinsonian symptoms, the causes for the lack of definite clinical symptoms despite widespread a-synuclein pathology in the nervous system, their relations to Alzheimer-type lesions, and the pathophysiologic impact of both pathologies remain to be further elucidated.

Introduction

Among proteinopathies, a heterogenous group of neurodegenerative disorders, characterized by intra- and extracellular accumulation of abnormal filament proteins, Lewy body (LB)-associated disorders, such as Parkinson disease (PD) and dementia with Lewy bodies (DLB) show protein inclusions in neurons and neurites (LBs and Lewy neurites/LNs), glia, and presynaptic terminals [1], with a-synuclein (aSyn) as their major component [for rev see 2]). Given the fundamental nature of the aSyn containing lesions, these and other disorders, such as autonomic failure, LB dysphagia, and multiple system atrophy (MSA) have been summarized as a-synucleinopathies [3,4]. PD or brainstem type of LB disease [5,6] is the most common neurodegenerative movement disorder in the elderly, with progressive degeneration of the dopaminergic nigrostriatal system and other neuronal networks caused by loss of pigmented neurons in the substantia nigra compacta (SNc) and many other subcortical nuclei associated with widespread occurrence of LBs and LNs in the brain and specific nuclei of the spinal cord. PD-related lesions are not confined to the central nervous system, but also involve autonomic nuclei, sympathetic ganglia, cardiac and pelvic plexuses, and nerves as well as adrenal medulla, salvary gland and skin [7-23], clearly indicating that PD is a multisystem disorder [for rev. see 2,8]. DLB, the second most frequent cause of dementia in the elderly after Alzheimer disease (AD), with the core neuropsychiatric features of fluctuating consciousness, visual hallucinations and parkinsonism, is morphologically featured by a variable burden of a synucleinopathy with (often widespread) cortical LBs and various degrees of AD-related pathology [5,6].

The distribution pattern of aSyn pathology within selectively vulnerable neuronal populations is considered to be intimately linked to the clinical dysfunctions seen in both disorders, aSyn lesions in the brainstem been mainly claimed to be responsibe for extrapyramidal motor symptoms, whereas cognitive impairment has been attributed to the limbic and neocortical spread of LB lesions [24-28]. Thus, PD and DLB are believed to represent phenotypes in a continuum within the spectrum of LB disorders, wherein the clinical manifestations predominantly depend on the anatomical distribution and load of aSyn pathology [6,13,29-31]. Despite clinical, biochemical and morphological similarities and dissimilarities, the relations between the two disorders have been discussed controversially [2,32-37]. Two morphological staging/classification systems are currently used for the assessment of the progressive regional distribution of aSyn pathology in PD and DLB [5,6,29,38], the applicability and clinical relevance of which has been critically discussed recently [39]. Both staging systems, the Braak hypothesis of LB staging in PD [29] and the

DLB consensus guidelines [5,6] were developed in non-population-based cohorts. The essentials and validity of these two systems will be critically evaluated based on recent literature and personal studies.

Staging of aSyn inclusion body pathology in sporadic PD

Based on semiquantitative assessment of aSyn-positive inclusions in 413 postmortem cases including 41 PD cases, 69 with aSyn inclusions and and 58 aged-matched controls, a hypothetic staging system of brain pathology indicating a predictable sequence with increasing severity throughout the brain and ascending progression has been proposed [9,29,40-42]. aSyn pathology was divided into six successive stages: The earliest lesions were seen in the lower medulla oblongata with a few LNs in the dorsal motor nucleus of the vagus nerve (DMV), in anterior olfactory structures, chiefly affecting the anterior olfactory nucleus embedded in the olfactory tract, and some aSyn-positive aggregates in preganglionic vagal axons [10], with the nucleus basalis of Meynert (NBM) and midbrain regions being preserved (Stage 1). More severe lesions in the DMV with extension to the caudal raphe nuclei and gigantocellular portions of the adjoining reticular formation, and some LNs in the noradrenergic locus ceruleus (LC) are seen in stage 2. These initial stages (observed in 7% of the cohort) were considered a(pre)symptomatic and may explain early non-motor (autonomic and olfactory) symptoms that preceed the somato-motor dysfunctions [43-46]. In stage 3, the LC, the central nucleus of the amygdala, the tegmental pedunculopontine nucleus and cholinergic nuclei of the basal forebrain including the NMB are the focus of cytoskeletal changes and neuronal depletions, the posterolateral and posteromedial parts of SNc showing pale bodies (precursors of LBs) [47] and LBs without neuronal loss, while the allocortex and neocortex are preserved. In stage 4, the anteromedial temporal limbic (transentorhinal) and mesocortex and amygdala are additionally affected. Stages 3 and 4 have been correlated with clinical motor symptoms (11% of their cohort). In stage 5, the lesions in the temporal mesocortex are more striking and from there progress to adjoining association fields of the temporal and prefrontal neocortex, while in stage 6, the lesions involve the neocortex, first affecting the high-order sensory association cortex and prefrontal areas, later progressing to the primary sensory and motor areas or involving the whole neocortex (Fig. 1). The cases with severe pathology (stage 5-6) accounting for 6% of their cohort, frequently show cognitive decline that relates to the severity of the neuropathologic stage [10,38]. In another retrospective study of 25 individuals (17 with PD, 8 with incidental aSyn inclusions) LB pathology and glial cytoplasmic inclusions in striatum were seen for the first time in stage 3 in

the medium-sized GABA-ergic spiny projection neurons that reach both the pallidum and SN reticulata (SNr), and at stages 5 - 6 in the large cholinergic interneurons [48].

Consensus pathologic guidelines for the diagnosis of DLB

According to the initial consensus pathologic guidelines, LBs are scored semiquantiatively according to the severity and anatomical distribution, separating brainstem predominant (PD), limbic/transitional and diffuse neocortical types, depending on the anatomical distribution of the aSyn-positive structures [5]. The revised consensus guidelines [6] proposed semiquantitative assessment of LB density, based on aSyn immunohistochemistry, in five cortical regions (Table 1a). However, the stage of AD pathology is usually not associated with the particular pattern of aSyn lesions [49]. A third pattern concentrated on aSyn pathology in cortical areas [50]. Considering the significance and clinical impact of concomitant AD-related pathology frequently seen in aged subjects with and without dementia, the revised consensus criteria for DLB have recommended to take it into account seriously [6] (Table 1b). This protocol was simplified by excluding the frontal region because of the common occurrence of occasional LBs in this regions in PD in the absence of dementia [51].

These guidelines did not provide definitie diagnostic criteria as it is sometimes mistakenly assumed, and were not included in the CERAD protocol, which is used for the semiquantitative evaluation of neuritic plaques and neurofibrillary tangles [52].

Studies to evaluate the reliability of aSyn-related stagings

The proposed staging procedure for aSyn pathology in PD rested, in part, on the assumption that incidental LB pathology is the first step along a disease continuum [42], but that sporadic PD, like most neurodegenerative disorders, is not a static but a dynamic biologic process and that so-called incidental lesions (LBs/LNs seen in subjects without PD related signs and symptoms) represent presymptomatic (subclinical) correlates of a pathologic condition ultimately leading to a manifest clinical disease [10,53-55].

Incidental LB disease (iLBD) is the term when LBs are found in the nervous system in subjects without clinically documented parkinsonism or cognitive impairment [54,56]. Epidemiological studies indicated that autonomic symptoms, REM sleep behavioral disorder and olfactory dysfunction may precede overt extrapyramidal motor symptoms by years [57-59], resulting from LBs and LNs in the enteric plexus [10,60], affection of lower brainstem nuclei [61,62] and the sympathetic cardiac nervous system [63]. Recent studies of iLBD cases

have shown a distribution of LBs similar to that in PD, involving one or multiple brain areas, some also with sparse LBs in limbic or temporal cortex (average Braak stage 2.7 ± 0.3) in comparison to definite PD cases with more numerous LBs in all regions and significantly higher Braak PD stage (average 4.4 ± 0.3). When both groups were taken together, a significant inverse correlation existed between neuronal densities in the three anatomical regions studied and the Braak PD stage [64]. Furthermore, there was decreased TH immunoreactivity in both the striatum and sympathetic epicardial nerve fibers in cases with incidental LB pathology compared to normal controls but not in the same extent as in PD [64,65]. On the other hand, incidental aSyn pathology may affect solely the LC and SN without affection of the medullary nuclei [66-69]. Incidental LBs are not considered as a normal aging phenomenon, whereas neurofibrillary tangles increase with age in the SN [70], and are associated with increasing neuritic AD stages [71]. These findings suggest that iLBD is likely a precursor to or preclinical form of PD, and the lack of symptoms is due to subthreshold aSyn pathology.

Some recent studies have largely confirmed this staging of LB-related pathology in sporadic PD, showing that all brains of subjects with clinical PD revealed aSyn-positive inclusions and neuronal losses in medullary and pontine nuclei and SN, and additional lesions in NBM (90-98 %), limbic cortex (50-60%), cingulate area (32-46%), frontal cortex (29-31%), and amygdala (25%), corresponding to LB stages 4 to 6 [3,66]. In a previous study, LBs in SN were found in 99.2% of clinico-pathologically confirmed PD cases [72]. LB pathology first appears in the ventrolateral part of SNc, spreads to the paranigral nucleus and then to the medial part, and finally to the dorsal part of SNc [73]. There is severe depletion of melanized neurons (45-66%) and of dopaminergic neurons immunoreactive for tyrosine hydroxylase (TH) (60-85%) in the A-9 group of SNc, particularly in the ventrolateral tier (91%) projecting to striosomal compartments of the striatum [74], followed by the ventromedial (71%) and dorsal parts (56%) [75]. The calbindin (CAB)-rich compartments show greater cell loss in the caudal and mediolateral region (98%) than the adjacent matrix. From there, it spreads to other nigrosomes and finally to the matrix along a caudorostral, lateromedial and ventrodorsal progression [76]. These changes differ from age-related lesions in the dorsal tier of SNc that is involved only in late stages of PD [75,77]. The A-10 group of dopaminergic neurons - ventral tegmental area, nucleus parabrachialis, and parabrachialis pigmentosus - projecting to the striatal matrix, thalamus [78], cortical and limbic areas (mesocortico-limbic system) [79] in PD show less severe involvement (40-50% cell loss), the retrorubral A-8 region containing only few dopaminergic but CAB-rich neurons, and the

central periventricular gray suffer little or no degeneration [80]. Others reported greater cell loss in LC (area A-6) than in SN in both PD and AD [81]. Morphometric studies showed a 35-41% reduction of pigmented SN cells, with severe loss of dopamine transporter (DAT)-immunoreactive neurons in older persons [82] and increase in the volume of these cells [83]. Some studies have estimated the neuronal loss as 4.3% per decade [83], while others have reported almost 10% [84]. Recent morphometric stereologic studies of the human SN revealed a significant loss of pigmented (-28.3%) and TH-positive (-36.2%) neurons in older controls compared to younger subjects, with hypertrophy of cells in older controls, interpreted as a compensatory mechanism to allow normal motor function despite cell loss. PD showed a massive loss of SN neurons with significant atrophy of remaining cells (20% of controls), but most of the examined cases were in the end stage of the disease [85].

A prerequisite of the proposed staging system of aSyn inclusion pathology is that the extent and severity of lesions increase as the disease progresses [41]. A study of 21 PD brains by six observers from five different institutions examining 11 different brain areas revealed highly significant inter- and intra-rater reliability and supported the suitability of the staging procedure of aSyn pathology for application in routie neuropathology and brain banking [86]. However, the reliability of this staging system has recently been challenged [3,49,66-68,87,88]. In Braak's cohort of 301 cases (including 176 clinical PD and 106 with incidental LB pathology), only 6.3% of PD brains diverged from the hypothetical staging scheme of aSyn pathology, with predominant involvement of olfactory structures and amygdala, and advanced concomitant AD-related neuritic pathology [10,41]. However, among 71 cases of PD from the London brain tissue bank only 53% showed a distribution pattern of aSyn compatible with the caudo-rostral spreading suggested by Braak et al [29] and 43% did not fit the predicted spread of aSyn inclusion pathology. The most frequently affected regions were SN and NBM (100 and 98.5%, respectively), followed by LC and DMV (97 and 92.9%, respectively). In 7% the DMV was not affected, although aSyn inclusions were found in SN and/or cortical regions [87]. On the other hand, in a 68-year-old woman with late-onset, dopa-responsive parkinsonism of almost 13 years duration, autopsy revealed severe neuronal loss with many LBs in DMV but only moderate neuron depletion (60%) in SNc without any LBs and moderate cell loss with diffuse aSyn cytoplasmic staining in LC, suggesting unusual manifestation of LB disease in clinically definite PD [60]. In an autopsy series of 260 elderly subjects including 71 cases of autopsy proven PD, 38 of DLB, 116 AD and 26 age-matched controls (with positive aSyn pathology in 51% of AD and 31% of controls), 30% of AD cases with multifocal aSyn pathology but without clinical EPS showed no involvement of the

medullary nuclei [66]. In another autopsy series of 60 autopsy-confirmed cases of PD (29 PD with dementia /PDD/ and 31 without dementia, mean age at death 82.5 years), some early PD symptoms were shown to occur already in rare cases with LB stage 2 (2.3%), eg., autonomic and bladder dysfunctions, sleeping disorders, constipation, orthostatic hypotension, and depression, and more often in stage 3 (15.0%), in which most patients clinically revealed stiffness, asymmetric rigidity, and mild hypomimia but no tremor. Stage 4 (50.0%) and stage 5 (31.7%) showed typical PD-related motor features [3,67]. Thirty-nine brains (65%) showed almost equal aSyn load in SN, NBM, LC and both DMV and gigantocellular reticular formation, while 11 brains (18.3%) revealed considerable aSyn lesions in SN, LC and NBM, but only mild involvement of DMV. In this material, the most frequently involved CNS regions were SN (96.7%), NBM (98%), and LC (96.7%), whereas the DMV was involved in 91.7%. Five brains (8.3%), despite definite involvement of SN, LC and NBM in four and additional cingulate gyrus and limbic cortex involvement in one each, showed no aSyn lesions and almost no neuronal loss in DMV. The latter cases clinically presented with rigid-akinetic and L-dopa responsive PD, with rest tremor in three and dementia in two cases (one each with frontal and limbic cortical involvement). Less frequently affected brain regions were the olfactory bulb (70%), CA 2/3 sector of hippocampus (39%), previously regarded as a means to differentiate diffuse DLB from PD [89], and cingulate gyrus and/or frontal cortex (31.6%) [67]. In general, DMV and SN were found to be equally susceptible nuclei, but structures even earler affected by aSyn pathology include the spinal cord, DMV, olfactory bulb and amygdala [11,29,42,90-92]. The fact that between 6.3 and even 47% of all clinical and autopsy-confirmed PD cases obviously do not strictly follow the proposed staging system of aSyn inclusion pathology and that in 7 to 8.3% the DMV was not involved despite definite aSyn pathology in higher brainstem or even cortical regions [67,68,87] suggests that the proposed ascending pathway may not be the only possible route of disease progression and simultaneous involvement of subcortical and cortical regions appears to be possible. In very few cases of DLB with severe AD-pathology, the amygdala develops aSyn pathology and neuronal loss prior to the brainstem nuclei, while depletion of cardiac nerves is not necessarily seen [93]. aSyn pathology beginning in the amygdala associated with AD [90,92,94] may show rostro-caudal spread to the entorhinal cortex and midbrain/brainstem regions. However, the reasons for such deviations from the frequently but not consistently observed caudo-rostral propagation and for sparing of medullar nuclei even in clinically manifested PD await further elucidation.

A recent study on the progression of pathology in longitudinally followed PD patients verified three different clinicopathologic groups: (1.) In a group of younger onset patients presenting with long clinical duration and LB distributions consistent with the Braak staging, brainstem LBs dominated in those surviving up to 5 years; by 13 years 50% of cases had a limbic distribution of LBs, and by 18 years, all had at least this pathologic subtype. (2.) About 25% of cases had an early malignant, dementia-dominant syndrome and severe neocortical disease consistent with DLB. (3.) The last group with older onset, shorter survival and more complex disease course showed higher LB loads, suggesting that widespread LB pathology either occurs at the onset of clinical disease or rapidly infiltrates the brain with frequent concomitant lesions, in particular more plaque pathology, supporting a more aggressive and linked phenotype. These data suggest that the different phenotypes cannot be differentiated by pathology alone and are also not consistent with a unitary concept of the pathogenesis of LB disease [95].

a-Syn pathology in the nervous system and clinical manifestations

Lewy body pathology in the central and peripheral autonomic system in a neurologically unremarkable elderly human population is not an infrequent finding [3,11,49,53,66,68,88,96-98], which was detected only in comprehensive studies of the whole nervous system. Comparisons between such studies should account on case selection and the methods used for detecting LBs [68,88,99-102]. Earlier studies showed LBs in the brains of 50 elderly persons without extrapyramidal symptoms [53], aSyn pathology in SNc in about 10% of neurologically unimpaired elderly persons [97] and in midbrain and limbic cortex in 31% of asymptomatic aged controls with a mean age of 82.0 years. These were referred to as iLBD. while multifocal aSyn pathology in10% of them corresponded to Braak LB stages 4 [66]. Among 241 autopsy cases without clinical evidence of neurologic disease (average age 78.7 years) from the the Mayo Clinic Tissue Registry (Rochester, MN, USA) 36 cases (15%) with incidental LBs were found [103]. Another study of aSyn pathology in 1241 consecutive elderly patients distinguished LB stage 0 (87.3%), stage 1 (incidental LBs, 12%), stage 2 (LBs without attributable clinical symptoms, 3.8%), stage 3 (PD without dementia, 8.1%), stage 4 (DLB transitional form, 2.1%), and stage 5 (neocortical DLB, 1.9%) [104], while in a single neurologically unimpaired subject, widespread and abundant aSyn pathology was detected [98], which was suggested to predict neither extrapyramidal symptoms (EPS) nor dementia. Among 98 elderly autopsy cases without PD-associated symptoms, aSyn pathology was found in the brain, spinal cord and peripheral autonomic system in 17.3% [11]. Among 208

autopsy cases from the MRC CFAS brain donor cohort aged 65+ years (almost 75% over 80 years old, 50% of them demented), 76 brains (36.5%) showed LBs. Only 51% of these conformed to the Braak LB staging, while 17% had aSyn pathology in a higher region which was absent in a lower region. A further 29% showed amygdala-predominant aSyn pathology. Six brains presented predominant neocortical aSyn pathology with minor involvement of amygdala and SN [49]. This population-based study showed that 80% of those with aSyn pathology conformed either to a DLB consensus/Braak stage pattern (51%) or to amygdala-predominant disease (29%). Amygdala-predominant aSyn pathology was therefore present in 60% of a DLB/Braak stage-conforming pattern. The remaining 20% did not fit into either system of aSyn progression - a previously unreported population group. A group in which aSyn pathology was predominantly neocortical, with minimal amygdala involvement and absent transentorhinal/cingulate brains (8%), corresponds to the diffuse cortical form of DLB [50,105]. The MRC CFAS study confirmes that aSyn frequently coexists with AD-type pathology, but suggests that there is no consistent hierarchy in the progression of the two disease processes [69]. In the hitherto largest autopsy series of 1720 individuals aged at death > 40 years from Kuopio, Finland, the total frequency of aSyn lesions was 14% [68]. 83% of them showed a distribution pattern of aSyn lesion comparable to the two current staging systems of PD and DLB, but 55% of subjects with widespread aSyn pathology (Braak PD stages 5-6) lacked clinical signs of dementia (MMSE >26) or EPS. Similarly, among those subjects that fulfilled the McKeith criteria for DLB and displayed only mild concomitant AD-related pathology, only 48% were demented and 54% displayed EPS. When only demented subjects were included in the analysis, the correlation between aSyn pathology and dementia was 85%. 17% of all cases showed deviations from the suggested caudo-rostral disease progression. One subject with EPS was found already in Braak PD stage 2, whereas none of the cases in stage 4 displayed EPS, and more importantly, no EPS had been reported in 55% of subjects who exhibited widespread aSyn pathology (Braak PD stages 5-6), as compared to the 14% previously reported [29]. These and other results suggest that the risk for EPS increases with disease progression though not to the same extent as previously believed. On the other hand, in large autopsy samples between 30 to 55% of elderly subjects with widespread aSyn pathology were neuropsychiatrically intact lacking clinical symptoms or were not classifiable [66,68,106].

Initial decline in cognition was postulated to occur already during stages 3 and 4, i.e. around the same time when initial manifestations of somatosensory and motor dysfunction appear. Among 88 subjects, dementia was observed in stage 3 (36%), 4 (67%), stage 5 (94%)

and in 100% in stage 6, indicating that increasing cognitive decline (decreasing MMSE scores) correlated with increasing aSyn stages [38], which was not confirmed by others [68,107-109]. In the hitherto largest autopsy study of aSyn pathology in humans,the percentage of demented persons increased from 0 to 50% between LB stages 3 and 6. However, when subjects with either EPS or dementia were included, 91 and 94%, respectively, were assigned to PD stages 5-6. This indicated that only when subjects with clinical symptoms were included in the analysis, the correlation between stage/severity of aSyn pathology and EPS and/or dementia was excellent in line with previous reports [68]. In an autopsy series of 330 elderly patiens with clinical parkinsonism (37.6% of which with dementia), only 1.6% of the demented patients (MMSE < 20) showed LB Braak stages 3-5, which were found in the majority of non-demented PD cases, while 35.5% of parkinson-dementia (PDD) cases revealed LB stages 4 or 5 with superimposed severe Alzheimer pathology (neuritic Braak stages V and VI). More than half of them showed a strong relationship between aSyn and tau pathologies, particularly in the limbic system. DLB with low or high-grade Alzheimer lesions were seen in 40% of PDD patients, but almost one-third of diffuse DLB cases, i.e. those with mild AD lesions restricted to amyloid plaques or tau pathology in the limbic system, did not show considerable cognitive impairment [110].

The clinical relevance of cortical aSyn pathology in relation to cognitive impairment is a matter of intense debate. Some authors have emphasized their key causative role [24-26,28], whereas others have reported abundant LB cortical lesions in non-demented PD patients [107] as well as in neuropsychiatrically unimpaired elderly subjects [68,98]. These data clearly indicate that detailed regional assessment of aSyn pathology, the inter- and intrarater reliability of which has recently been reviewed [39], cannot reliably predict the clinical status observed *intra vitam* [88]. The neuropathology of PD with and without dementia and DLB shows both similarities and slight differences. Morphology and immunohistochemistry of cortical and subcortical LBs and the ascending spreading pattern of aSyn pathology do not significantly differ between both subtypes, the late cortical stages 5 and 6 of LB pathology suggesting overlap or transition between PD and DLB [2,3,66,111], although DLB often has higher density of cortical LBs and AD-lesions than PDD [112]. The SN and other subcortical nuclei in DLB show variable neuronal loss often indistinguishable from sporadic PD, except for an occasionally more severe loss in the ventro(dorso)lateral tier compared to predominant cell loss in the medioventral parts of SNc in PD and more frequent involvement by aSyn deposits of the limbic system, in particular the CA 2/3 subarea of the cornu Ammonis in DLB than in PD/PD (79 vs 36%) [2]. A major morphologic difference is the significantly more

frequent and severe load with diffuse amyloid plaques in the striatum in DLB, irrespective of the severity of cortical AD-type lesions, while non-demented PD cases are virtually free of Aß pathology as is the globus pallidus [113-115]. There are neither correlations between LB density in any brain area and neuritic Braak AD stages or frequency of neuritic plaques [116], nor between LBs in cortex and SN, suggesting that DLB should not be considered a severe form of PD. Whereas LB densities, in general, cannot separate DLB from PD/PDD, the severity and duration of dementia appears to be related to both increased hippocampal LB densities and neuritic plaque grade. A screening algorithm suggesting that LB density thresholds in parahippocampus may distinguish demented from nondemented PD cases independent from other pathologies [117] awaits further confirmation. However, individuals can show significant cognitive disturbance with no or minimal cortical LBs and, converesely, widespread cortical LB pathology without essential cognitive decline [38,107,118]. In the large Finish autopsy cohort 56% of those subjects where limbic/diffuse neocortical aSyn pathology combined with mild to moderate AD-related changes remained cognitively intact. However, when only demented subjects with severe AD-related pathology (neuritic Braak stages V and VI), were examined, 85% were assigned to a high likelihood category of DLB and all of them were demented [68]. Hence, in cognitively impaired subjects there is a good correlation between dementia and particular pathologies.

In conclusion, recent clinico-pathologic studies confirm that the current staging / categorization systems for can readily be applied to most of the subjects when assessing regional distribution and progression patterns of aSyn pathology, although in a certain percentage of cases this caudo-rostral propagation pattern suggested for PD cannot be confirmed. In such cases the pattern of relevant lesions may have been modified by other coexisting pathologies or genetic factors [92,119-121]. Various clinical, biochemical and morphological overlaps between PD, DLB and AD including co-localization of tau and aSyn epitopes in LBs suggest that the process of LB formation is triggered, at least in part, by AD pathology [2,122,123]. Deposition of tau can be demonstrated in a proportion of LBs, being greatest in neurons vulnerable to both LB and NFT formation, such as in LC, NBM and amygdala [124,125]. This suggests that aSyn and tau may be related to several pathologic processes (bystander effect), which explains the frequent overlap between synucleinopathies and tauopathies [126,127]. The collision of two or more processes may occur in the same brain region or even in single cells in the human brain, eg., in LRRK2 mutations [128] and in animal models of PD [129], with association of phospo-tau and aSyn in both NFTs and LBs [130] and *in vitro* promotion of tau aggregation by aSyn and *vice versa* [131]. Others have

suggested that amyloid rather than tau enhances aSyn pathology in human brain and transgenic mice [121,132]. These interactions highlight the interface between these and other misfolded proteins [127,133] and may represent molecular mechanisms in overlapping pathology of PD/DLB and AD [134,135], together with recent biochemical data on tau and ß-amyloid [136] challenge the view of PD and DLB as distinct entities.

The recent MRC CFAS study found no evidence for preponderance of amygdala-predominant aSyn pathology over the prototypical DLB/Braak hierarchy in terms of an association with AD [49]. According to these authors, this does not support the proposed hypothetical link between aSyn in the amygdala and AD pathology [90,92], and was explained by the fact that the studies from which these hypotheses emerged included only clinically referred, i.e. selected cases.

On the other hand, in retrospective studies of unselected autopsy cohorts up to 50% of cases displaying abundant aSyn pathology had been reported to be clinically intact without neuropsychiatric deficits. It has been suggested that the key lesions may develop a considerable time prior to the appearance of clinical symptoms [75], but the duration and progression of this "preclinical" phase is still under discussion. According to functional neuroimaging studies this preclinical periods range from 4.6 to 6.6 years, with an annual decline of striatal dopamine uptake of 8-10% and of DAT between 5.7 and 6.4 years or 10 to 13 %. Higher nigrostriatal dopamine loss has been suggested in early than late onset PD [137]. Reduction of striatal dopamine by 57-80% [138] and DAT loss of 56% or approximately 50% of nigral dopaminergic neurons cause motor symptoms [139]. Thus, about 50% of dopaminergic striatal innervation appears to be sufficient for normal motor function [140]. Striate dopamine release was 60% reduced in PD patients, whereas in the frontal cortex it was within normal range, indicating that it remained preserved even in severe stages of the disease [141]. Decreased DAT ultimately results in increased dopamine turnover preposing towards the occurrence of motor complications as PD progresses [142]. However, recent studies in both movement disorders and dementing processes demonstrated that some subjects may tolerate substantial amounts of both aSyn and tau pathology without definite clinical manifestation, suggesting considerable compensatory mechanisms of the aging brain [143-148]. Recent FDG- PET studies in PD showed only a short metabolic preclinical period [70]. It should be considered, however, that the biological significance and clinical impact of abnormal aSyn aggregations are not yet clear. Like other fibrillary proteinaceous inclusions, such as NFTs or Pick bodies, they may represent end products of reactions to higherto unknown neuronal degenerative processes [149]. The question whether LBs and other aSyn

aggregates are cytotoxic and lead to neuronal death due to production of oxidative stress, mitochondrial energy deficit and other noxious factors or are cytoprotective still remains unresolved [150-154]. Biophysical studies have suggested that rather the protofibrillary than the fibrillary form of aSyn is cytotoxic [155-157], whereas the LBs and LNs composed of fibrillary aSyn which are typically observed at autopsy, may be the structural manifestation of a cytoprotective response designed to confine and to eliminate cytotoxic proteins or abnormal cytoskeletal elements [149,158-160]. There is no correlation between the density of LB formation and neuronal cell loss [161], and the comparatively low number of neurons containing LBs in any brain region would not be expected to result from altered synaptic function. Nevertheless, significant intracellular protein aggregation, such as LB formation, are pathologic processes, reflecting changes in the cellular environment that may finally contribute to dysfunction of the involved cells. Recent studies showed development of LBs in grafted neurons in subjects with PD, suggesting host-to-graft propagation [162].

Existing definitions and classification systems should be based on an understanding of the underlying pathologic process which, in the case of synucleinopathies is still incomplete. Therefore, in view of the caveats discussed above and the inter- and intraindividual biological variabilities, the neuropathologic staging procedures are instruments being far from perfect [163,164]. Although recent studies indicate that LB pathology is indeed progressive, the assessment of regional distribution patterns of aSyn pathology may either evaluate a stage of degeneration or conversely monitors the level of functional neuroprotection, concluding that the topographic mapping of aSyn deposition may be of questionable value, because its is unclear whether LB pathology is the primary (or solely relevant) pathology in PD and related disorders [68]. If it is the synucleinopathy that characterizes and drives idiopathic PD (and DLB) [165], the question arises about the degree of lesional density that has to be reached to induce clinical symptoms. Although it has not been proved yet, the presence of abnormal filaments or protein aggregations, which have been observed in PD to develop first in axons as LNs [16,166], may finally damage the parent nerve cell by interfering with axonal transport [10,124,167-170]. Keeping all these pros and cons in mind, one has to conclude that if robust correlations between clinical course and morphologic changes will be confirmed by future prospective clinico-pathologic studies, the neuropathologic staging/classification systems will need to be revised accordingly.

Figure Legend:

FIGURE 1. Progress and distribution pattern of PD-related neuronal pathology. *ab* accessory basal nucleus of amygdala, *ac* accessory cortical nucleus of amygdala, *ad* anterodorsal nucleus of amygdala, *am* anteromedial nucleus of thalamus, *an* abducens motor nucleus, *ba* basal nucleus of amygdala, *bn* basal nucleus of Meynert, *ca1* first Ammon's horn sector, *ca2* second Ammon's horn sector, *ca* caudate nucleus, *cc* corpus callosum, *ce* central nuclei of amygdala, *cg* central grey of mesencephalon, *cl* claustrum, *co* cortical nuclei of amygdala, *cr* central nucleus of raphe, *db* nucleus of the diagonal band, *dm* dorsomedial hypothalamic nucleus, *dr* dorsal nucleus of raphe, *ds* decussation of superior cerebellar peduncles, *dv* dorsal nuclear complex of vagal nerve, *en* entorhinal region, *fn* facial motor nucleus, *fo* fornix, *gi* gigantocellular reticular nucleus, *gr* granular nucleus of amygdala, *hn* hypoglossal motor nucleus, *in* infundibular nucleus, *ir* intermediate reticular zone, *lc* locus coeruleus, *ld* laterodorsal nucleus of the thalamus, *lg* lateral geniculate body, *li* nucleus limitans thalami, *lt* lateral nuclei of the thalamus, *md* mediodorsal nuclei of thalamus, *me* medial nuclei of amygdala, *mf* medial longitudinal fasciculus, *mg* medial geniculate body, *ml* medial lemniscus, *mm* medial mamillary nucleus, *ms* medial septal nucleus, *mt* mamillothalamic tract, *mv* dorsal motor nucleus of vagal nerve, *oi* oliva inferior, *os* oliva superior, *ot* optic tract, *pe* external pallidum, *pf* parafascicular nucleus, *ph* posterior hypothalamic nucleus, *pi* internal pallidum, *po* pontine grey, *pr* praepositus nucleus, *pu* putamen, *pv* paraventricular nucleus, *re* reticular nucleus of the thalamus, *rm* nucleus raphes magnus, *ru* nucleus ruber, *sb* subiculum, *sc* superior cerebellar peduncle, *sf* solitary fascicle, *so* supraoptic nucleus, *sn* substantia nigra, *sp* subpeduncular nucleus, *st* nucleus of the stria terminalis, *sn* subthalamic nucleus, *te* transentorhinal region, *tl* lateral tuberal nucleus, *tm* tuberomamillary nucleus, *tp* tegmental pedunculopontine nucleus, *vl* ventro-lateral nuclei of thalamus, *vm* ventromedial hypothalamic nucleus, *vn* vestibular nuclei, *vt* dopaminergic nuclei of ventral tegmentum (paranigral nucleus and pigmented parabrachial nucleus), *zi* zona incerta.

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Table 1a: Consensus pathological guidelines for scoring cortical LB deposition

Cortical region	Brodmann area	Anatomy	Score		
Entorhinal cortex	29	Medial flank of collateral sulcus	0	1	2
Cingulate gyrus	24	Whole gyral cortex	0	1	2
Mid-frontal cortex	8/9	Lateral flank of superior frontal sulcus	0	1	2
Mid-temporal cortex	21	Inferior surface of superior temporal sulcus	0	1	2
Inferior parietal lobule	40	Lateral flank of parietal sulcus	0	1	2

Cortical Lewy body score:

0-2 Brainstem-predominant, 3-6 Limbic or 'transitional', 7-10 Neocortical

For each region, Lewy bodies are counted from the depth of the sulcus to the lip. Counts are not made over the crest of the gyri except for the cingulate gyrus. Lewy bodies are predominantly located in deeper cortical layers (layers 5 and 6). In each region a count of up to 5 Lewy bodies in the cortical ribbon gives a score of 1 in the table. Counts greater than 5 score as 2. The sum of the five areas is used to derive the category of cortical spread (maximum score 10).

Table 1b: Neuropathologic diagnosis of DLB

	Alzheimer type pathology		
Braak stage:	0-II	III-IV	V-VI
LBD			
Brainstem predominant ()	low	low	low
Limbic (transitional)	high	intermediate	low
Diffuse (neocortical)	high	high	intermediate