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REVIEW

Neuropathology underlying clinical variability in patients with synucleinopathies

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Abstract Abnormal aggregates of the synaptic protein, α-synuclein, are the dominant pathology in syndromes known as the synucleinopathies. The cellular aggregation of the protein occurs in three distinct types of inclusions in three main clinical syndromes. α-Synuclein deposits in neuronal Lewy bodies and Lewy neurites in idiopathic Parkinson's disease (PD) and dementia with Lewy bodies (DLB), as well as incidentally in a number of other conditions. In contrast, α-synuclein deposits largely in oligodendroglial cytoplasmic inclusions in multiple system atrophy (MSA). Lastly, α-synuclein also deposits in large axonal spheroids in a number of rarer neuroaxonal dystrophies. Disorders are usually defined by their most dominant pathology, but for the synucleinopathies, clinical heterogeneity within the main syndromes is well documented. MSA was originally viewed as three different clinical phenotypes due to different anatomical localization of the lesions. In PD, recent meta-analyses have identified four main clinical phenotypes, and clinicopathological correlations suggest that more severe and more rapid progression of pathology with chronological age, as well as the involvement of additional neuropathologies, differentiates these phenotypes. In DLB, recent large studies show that clinical diagnosis is too insensitive to identify the syndrome itself, although clinicopathological studies suggest variable clinical features occur in the different pathological forms of this syndrome (pure DLB, DLB with Alzheimer's disease (AD), and AD with amygdala predominant Lewy pathology). The recognition of considerable heterogeneity within the synucleinopathy syndromes is important for the identification of factors involved in changing their pathological phenotype.

Keywords α-Synuclein · Alzheimer's disease · Dementia with Lewy bodies · Multiple system atrophy · Parkinson's disease

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Overview

α-Synuclein is a 140 amino acid protein that forms pathological inclusions in idiopathic Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and other rarer clinical disorders (e.g., neurodegeneration with brain iron accumulation type 1 and other neuroaxonal dystrophies). The three major pathological forms of α-synuclein-containing inclusions are neuronal Lewy bodies (Fig. 1a) and Lewy neurites [156], oligodendroglial cytoplasmic inclusions [55] (Fig. 1b) and axonal spheroids (Fig. 1c) [120], although neuronal and glial intranuclear inclusions and neuronal cytoplasmic inclusions of a number of morphological types are also seen in MSA. Because these disorders have abnormal aggregations of α-synuclein, they are known collectively as synucleinopathies [155]. Despite all aggregating α-synuclein protein in the nervous system, the solubility [26] and cellular location of the protein varies between disorders, along with the neuronal populations affected [77, 155]. It is

this latter feature which impacts most on the clinical phenotypes observed.

In this review, we will concentrate on the three main types of synucleinopathies from a clinical perspective, and also discuss rarer disorders depositing abnormal α-synuclein as well as overlapping neurodegenerative diseases, like Alzheimer's disease (AD) which often also has pathological inclusions of α-synuclein [68]. Intuitively, disorders with neuropathology in different cellular structures in different regions of the nervous system are likely to have different clinical syndromes. Even among these syndromes with common underlying pathology, clinicians increasingly recognize that there is considerable phenotypic variability. This has become especially apparent in longitudinally followed cases, and a number of careful clinicopathological studies have begun to identify the underlying neuropathological substrates for this clinical variability within the different synucleinopathies. The object of this review is to evaluate current concepts and our experience regarding the pathological substrates that account for any clinical variability within the main synucleinopathies.

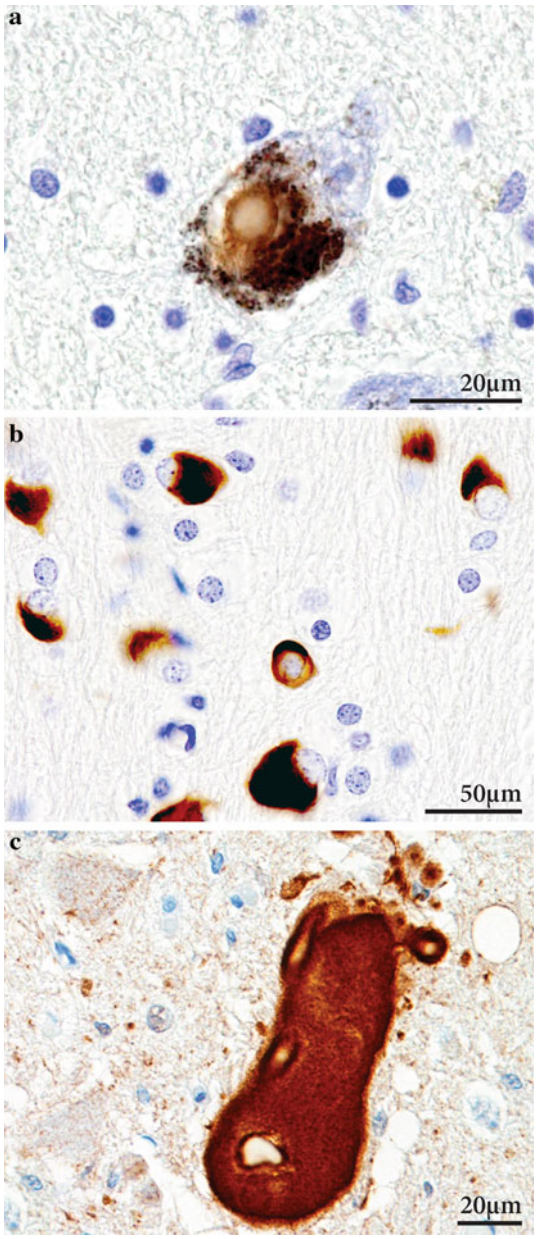

Fig. 1 Main pathological inclusions observed in synucleinopathies. **a** α-Synuclein-immunoreactive Lewy body in a pigmented substantia nigra neuron. **b** α-Synuclein-immunoreactive oligodendroglial cytoplasmic inclusions in the pons. **c** α-Synuclein-immunoreactive axonal spheroid in the pons

Lewy body disorders

The two synucleinopathy syndromes that are diagnosed by the presence of Lewy bodies and Lewy neurites (known collectively as Lewy-related pathology or LRP) are PD [35] and DLB [108]. In the majority of patients, these two main synucleinopathies are easy to differentiate clinically by the predominance of extrapyramidal motor features in patients with PD [76] and dementia in DLB [108]; however, in some patients, dementia and extrapyramidal signs occur in close succession, prompting debate about their nosology. For research purposes, cases are classified as DLB if dementia occurs within 12 months of the parkinsonian features, but as PD with dementia (PDD) if dementia occurs a year or more after a clinical diagnosis of PD [43, 108]. In actual clinical practice, a diagnosis is made based on the preponderant clinical features. The separation between PDD and DLB is considered by some to be artificial, since such a separation implies that the two clinical syndromes have different anatomical substrates, which may ultimately have different therapeutic challenges, and there is little difference in the distribution or severity of LRP between PDD and DLB [1, 163].

The pathological progression of LRP in both PD are DLB is thought to occur in a similar stereotypic fashion [17, 18, 90], although this is still a matter of debate [24, 25, 78, 81] and research [5, 10, 85]. There is no doubt that in many patients with severe clinical forms of PD and DLB, there is widespread LRP throughout the nervous system in selectively affected neuronal populations (Table 1) [35]. In a proportion of patients, LRP is largely confined to vulnerable brainstem structures, although forebrain and limbic regions are most commonly involved by end-stage disease (Table 1). Regardless of the debate on the pathological progression of LRP in PD and DLB, all studies show that at autopsy patients have quite variable degrees of LRP often in diverse regions of the nervous system, a finding that may account for at least some of the observed clinical variability.

Table 1 Comparison of pathological staging schemes for PD and DLB [35]

Braak stages for PD	Kosaka stages for DLB
Braak stages 1–2 (preclinical)	Brainstem Lewy body disease
Vagal dorsal motor nucleus	Vagal dorsal motor nucleus
Lower raphe nuclei	Raphe nuclei
Locus coeruleus	Locus coeruleus
	Substantia nigra, pars compacta
Braak PD stages 3–4 (clinical PD)	Transitional Lewy body disease
Substantia nigra, pars compacta	Amygdala, basal nucleus of Meynert
Amygdala, basal nucleus of Meynert	Intralaminar thalamic nuclei
Intralaminar thalamic nuclei	Olfactory and limbic cortices
Olfactory and limbic cortices	
Braak PD stages 5–6 (end-stage PD)	Diffuse Lewy body disease
Temporal cortex	Temporal cortex
Frontal cortex	Frontal cortex
Parietal cortex	Parietal cortex

Table 2 Clinical features of PD subtypes identified by cluster analyses [170]

Feature	Early-onset	Tremor dominant	Postural instability and gait dominant	Old onset
Estimated percentage	25–30%	15–25%	15–25%	25%
Average onset age	~50	~60	~60	~67
Progression	Slow	Intermediate	Intermediate	Rapid
Motor impairment	Mild	Intermediate	Intermediate	Severe
Axial impairment	No	No	Yes	Yes
Cognitive impairment	No	No	Yes	Variable

Pathological variability in Lewy body parkinsonism

PD is considered a relatively homogeneous clinical syndrome diagnosed by the presence of two of four cardinal signs (i.e. bradykinesia, rigidity, resting tremor, gait instability) that are responsive to levodopa therapy [58]. It is pathologically diagnosed when Lewy bodies are found in association with the loss of substantia nigra neurons [35], and it is the experience of the authors that, for the majority of longitudinally followed cases with PD, LRP infiltrates the nervous system in the stereotypic fashion described in Table 1 [6, 40, 65, 66, 95, 148].

The clinical definition of PD encompasses a relatively broad spectrum of motor impairments, and for many patients, non-motor manifestations become considerable over time [72]. Such diverse clinical features contribute to individual patient variability [76], and a number of large clinical studies have assessed this variability using cluster analysis to define more clinically homogeneous subtypes of PD patients likely to share pathologic and genetic features [170]. Meta-analysis of these studies has highlighted four main PD subtypes based on the age of onset, severity and type of motor impairments, rate of progression, and presence or absence of significant cognitive impairment (Table 2).

A number of recent clinicopathological studies have assessed the progression of pathology in some of these PD subtypes and observed subtle pathological differences. In a study that expressly tried to match these subtypes [148], the relative patterns and severity of LRP pathology were remarkably similar for both the early-onset and tremor dominant groups, although the average disease duration was 10 years longer for the early-onset group (22.5 vs. 13.5 years). This suggests that the *rate* of LRP formation differs substantially between those with an earlier versus later onset of PD (Fig. 2). Prospective assessment of PD patients to autopsy, excluding those with early onset, shows the progression of LRP in such typical cases is consistent with Braak PD staging [18] (Table 1), where brainstem LRP dominates in those surviving to 5 years, by 13 years 50% of cases have a transitional distribution, and by 18 years all have at least this pathological phenotype [65, 66]. In patients with non-tremor-dominant postural instability and gait dominated PD there are significantly more cortical Lewy bodies and amyloid β plaques compared with tremor dominant or younger onset patients [148]. These data show that both the rate of LRP deposition and the additional deposition of amyloid plaques correlate with different clinical phenotypes in PD. Recent data suggest

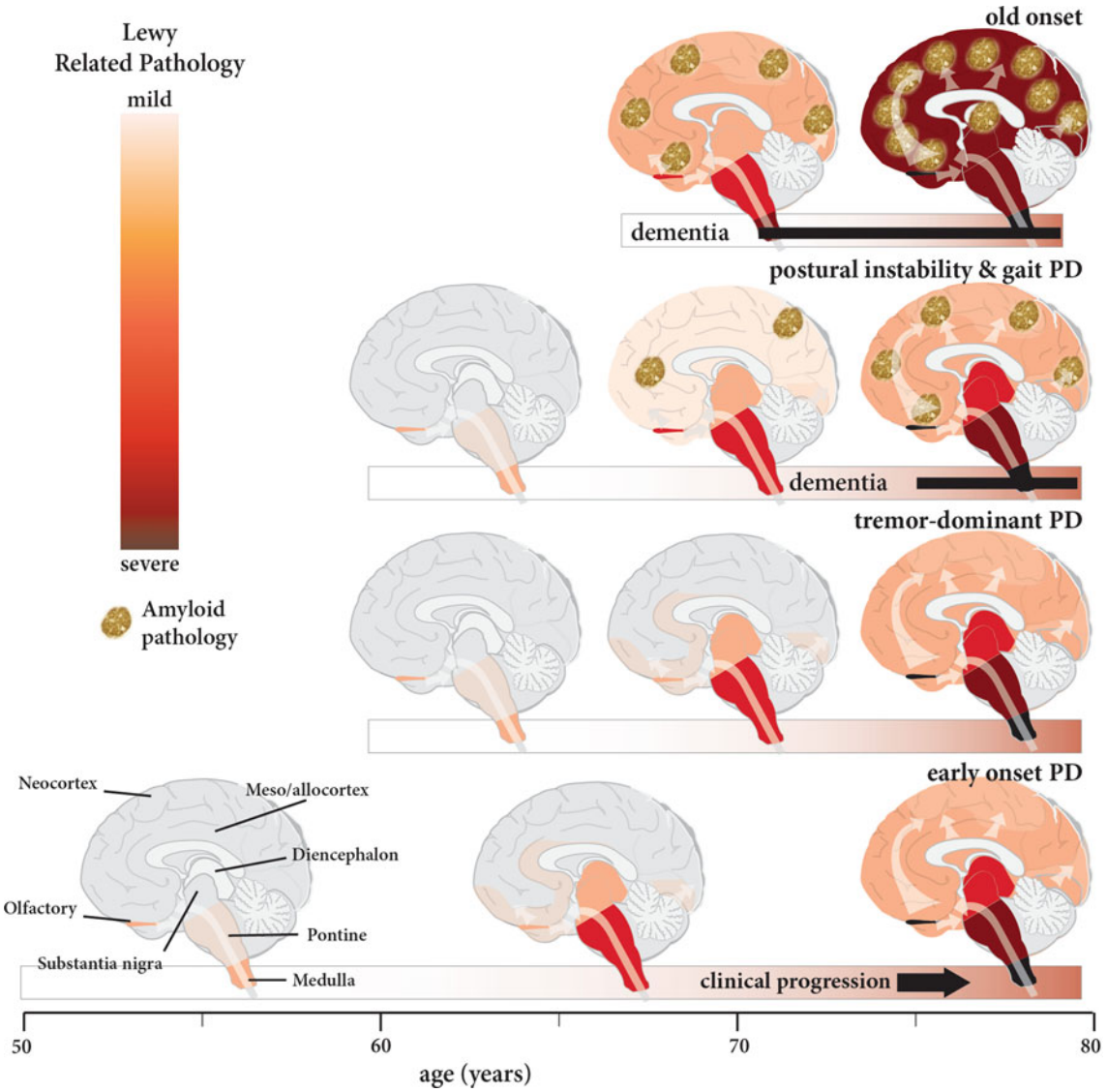

Fig. 2 Cartoon of the amounts and progression of pathology in the four major clinical phenotypes of PD with Lewy-related pathologies

that the severity of amyloid deposition in such cases is less than that observed in cases with dominant dementia [67].

In both retrospective [29, 93, 148] and prospective [65, 66] study designs, another major group identified has an older onset and more complex disease course, with shorter survival and more rapid cognitive decline due to an increased rate of progression. These clinically overlapping patients have higher amounts of cortical LRP and additional neuropathologies, particularly AD pathologies (Fig. 2; Table 2). Retrospectively assessing PD patients with dementia [6, 29, 70, 93, 148] reveals up to tenfold higher amounts of cortical LRP as compared to those without dementia and a correlation between the severity of LRP and AD pathology in such patients. The more rapid course and higher amounts of pathological deposits in these cases with additional neuropathologies suggests an even faster rate of LRP deposition that appears to be linked to multiple pathologies in older onset PD patients (Fig. 2). These cases have similarities to those described below with a dementia dominant phenotype.

A comment on LRP in genetic forms of PD

Genetic mutations can occur in either families or less commonly in sporadic patients with clinically typical PD and LRP (Table 3) [57]. Although the first gene identified with PD was α-synuclein (*SNCA*, Table 3), mutations and multiplications in this gene are rare and cause an earlier onset form of PD with increased LRP deposition (Fig. 3a, b; Table 3) [57]. Other very early-onset forms of clinical PD

Table 3 Genetic forms of PD [35]

Gene name	Chromosome location	PARK designation	Synucleinopathy
Typical PD			
LRRK2	12q12	PARK8	LRP
GBA	1q21		LRP
Earlier onset PD			
SNCA	4q21	PARK1/4	Increased LRP
Young onset recessive PD			
PRKN	6q25.2–q27	PARK2	None
UCHL1	4p14	PARK5	Not enough cases
PINK1	1p36	PARK6	Not enough cases
DJ1	1p36.23	PARK7	Not enough cases
ATP13A2	1p36	PARK9	Not enough cases
PLA2G6	22q13.1	PARK14/NBIA2	LRP, axonal spheroids
PANK2	20p13	NBIA1	Axonal spheroids

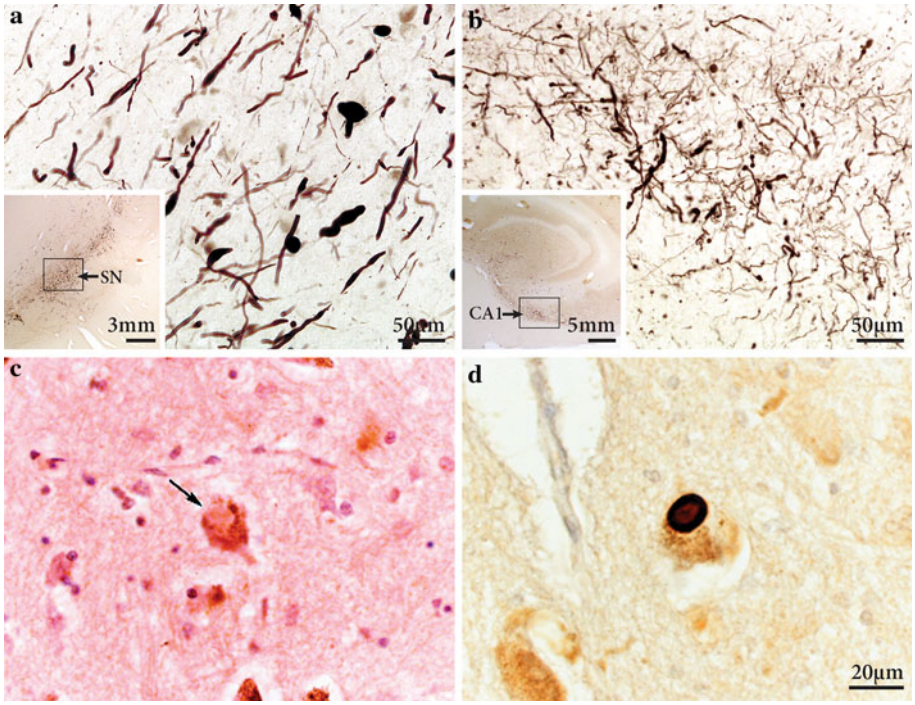

Fig. 3 Lewy-related pathologies in genetic forms of clinical PD. Thick sections of the midbrain (**a**) and hippocampus (**b**) from a patient with an A53T α-synuclein gene mutation stained immunohistochemically for α-synuclein with nickel enhancement. In addition to Lewy bodies, substantial numbers of Lewy neurites are easily seen at both low (*insets*) and higher magnification in these cases. Remaining pigmented neurons can also be seen in the substantia nigra (**a**). Thin sections of a fetal mesencephalic neuronal graft transplanted 11 years before death stained with hematoxylin and eosin (**c**) and S129 phospho-α-synuclein immunohistochemistry. Neurons from the fetal mesencephalic neuronal graft have eosinophilic Lewy bodies in neuromelanin-containing neurons (**c**) and show immunoreactivity for phospho-α-synuclein (**d**)

are largely due to a variety of recessive gene mutations, although there are limited autopsy studies on these subtypes of PD (Table 3) [57].

The most common gene mutation causing typical PD with LRP occurs in the leucine-rich repeat kinase 2 gene (*LRRK2*, Table 3) [57]. LRRK2 is a large, multidomain GTPase/kinase protein that has altered signaling in PD [64]. Because α-synuclein within LRP is phosphorylated and LRRK2 is a kinase, there is speculation that LRRK2 may play at least an indirect role in α-synuclein phosphorylation [64]. Further research is required to confirm any role for LRRK2 in LRP.

Some patients with neuronal Gaucher's disease, which is caused by homozygous, loss of function mutations of the acid β-glucosidase gene (*GBA*, Table 3) with resultant glucosylceramide accumulation, also suffer from parkinsonism with underlying α-synuclein-immunoreactive cortical and brain stem-type LRP [151]. Furthermore, several studies have identified heterozygous GBA mutations, as the most common genetic risk factor for LRP in different populations [28, 118, 122, 151]. Patients carrying heterozygous GBA mutations clinically present with typical PD associated with widespread LRP (Table 3) [118]. Data from cellular and in vivo models indicate a mechanistic link between GBA mutations and increased risk of LRP by demonstrating that GBA mutants promote α-synuclein accumulation [30].

A comment on LRP following therapeutic fetal grafts in patients with PD

Lewy-related pathology has recently been described in brain structures that are the product of modern neurosurgical treatments, specifically, fetal brain implants for the treatment of PD [88, 97, 98]. In fetal implants that developed LRP (Fig. 3c, d), a significant time lag is required (over 9 years); albeit a considerably shorter time than would be expected in anatomically appropriate vulnerable neuronal populations, such as dopaminergic neurons of the pars compacta of the substantia nigra. This has led to the speculation that α-synuclein is transmissible from cell-to-cell, with abnormal host α-synuclein triggering changes in conformation and solubility in donor cells through a templating process similar to that of prions [20]. That α-synuclein can be released from one cell and taken up by another cell has now been shown to occur in cell culture and animal models [31, 34, 94], and it has been suggested that the stereotypic spread of LRP in PD reflects cell-to-cell "spread" of a pathogenic abnormal conformer of α-synuclein [71].

Pathological variability in dementia syndromes that have Lewy bodies

It is generally unappreciated how pervasive LRP is in elderly patients with a dominant dementia syndrome, and it appears to be somewhat forgotten that most patients with a dominant dementia syndrome have cortical amyloid deposition [110, 136]. It is now known that LRP occurs in the amygdala in the majority of patients with clinically and pathologically confirmed AD [68] with the proposal that such cases should be considered a distinct clinicopathological entity [96, 167]. In addition to this restricted form of LRP in AD, more widespread deposition also occurs in a similar distribution pattern to that seen in PD, and such cases are considered to have DLB [108]. Despite considerable research and now better-known diagnostic criteria for DLB [108], very large autopsy series show that there is a very low diagnostic sensitivity for the clinical syndrome of DLB in dementia patients [115, 116]. This is even true for the diffuse cortical subtype of DLB which can have considerable LRP (Table 1) [115, 116]. Unfortunately, this means that the pathological forms of DLB can not be accurately identified clinically, even by highly experienced clinicians. The low accuracy of clinically diagnosed DLB has been shown to relate to the severity of dementia at examination, with those with more severe dementia often considered to have DLB [102, 115, 116]. Autopsy-confirmed DLB therefore remains clinically under-diagnosed in patients with milder dementia and over-diagnosis of DLB in patients with severe dementia who are more likely to have severe AD despite several cardinal features of DLB at this end-stage [115]. In addition, many older patients have more than one neurodegenerative syndrome [47, 79, 106, 124, 136, 137]. For this reason, the ascertainment of DLB remains problematic and any clinical subtyping even more difficult in current clinical series without autopsy confirmation. In prospective series comparing DLB to AD, diagnostic accuracy is higher if the severity of both LRP and AD pathology is taken into consideration [51]. Many of the clinical studies on DLB without autopsy confirmation need to be reconsidered in the light of such knowledge.

A number of retrospective clinicopathological studies of cases with dominant dementia and LRP have noted considerable pathological variability and assessed their clinical correlates. In such pathological studies, LRP cases are divided into those with coexisting AD (defined by the severity of tau neuritic pathology [108]) and those without excessive tau neuritic pathology, and the distribution and severity of LRP considered. This pathological differentiation identifies four different subtypes of cases, two of which have either more or less overlapping LRP with AD, as well as cases with more pure LRP or AD (Table 4). As discussed previously, the prevalence of LRP in patients with clinical and pathological AD is high, with amygdala LRP found in approximately 60% of cases [68]. Note that the vast majority of LRP cases with dominant dementia also have amyloid deposition [33, 36, 52, 70] and that, although cases with clinical PD can have AD (see above), in most PD cases, there is insufficient AD pathology for a definitive diagnosis.

Several retrospective clinicopathological studies of dementia cases with LRP suggest that some clinical features differ between the different pathological subtypes (Table 4). Pure DLB appears to have a clinical picture more similar to the dementia phenotype of PD [43] than to AD, with initially more severe executive dysfunction compared with memory deficits [91]. A high proportion of

Table 4 Clinical differences between cases with different pathological combinations of LRP and AD

Feature	Pure DLB	DLB + AD	AD + amygdala LRP	Pure AD
Severity of amyloid β deposition	High	High	High	High
Severity of tau deposition [177]	Low	High	High	High
Severity of LRP [167]	Highest	Intermediate	Low	Absent
Frequency of ApoE-4 [162]	NA	~50%	NA	~35%
Frequency of GBA mutation [28]	28%	NA	NA	10%
Odds for male gender [117]	2.9	2.9	NA	0.66
Odds for depression [101]	NA	3.83	8.56	0.96
Memory function [91]	Initially preserved	Poor	Poor	Poor
Executive function/ attention [91]	Poor	Poor	NA	Initially preserved
Functional decline [91]	Steady	Rapid	NA	Steady
Median survival and survival after dementia [183]	NA	78 and 7.3 years, adjusted for gender and ApoE	NA	85 and 8.5 years, adjusted for gender and ApoE

NA not available

heterozygous mutations in the *GBA* gene is found in this pathological phenotype [28]. A more rapid functional decline and mortality is observed in patients with DLB + AD [91, 183], while a high rate of depression occurs in patients with AD + amygdala LRP [101]. Patients with pure AD are more likely to be in older females than those with additional DLB [117, 183]. These studies show that variability in the distribution and severity of LRP in dementia cases impacts on clinical phenotype.

A comment on incidental LRP

Lewy-related pathology are detected in the nervous system of neurologically normal elderly individuals with a reported frequency of about 10% for those over age 60 years using classic histologic methods [46, 61], but twice that amount for studies using α-synuclein immunohistochemistry [105, 135, 141, 192]. The distribution of LRP follows the general distribution seen in PD and DLB [18] and includes involvement of sympathetic and parasympathetic central and peripheral nervous system, olfactory bulb and related olfactory cortices, as well as vulnerable brainstem and basal forebrain nuclei, including the amygdala [11, 15, 37, 105, 126, 135, 141]. In contrast to PD and DLB, the density of LRP is usually much less than in symptomatic individuals and it is typically not associated with neuronal loss or reactive gliosis, although in some retrospective forensic series, the severity of LRP appears to be more marked [135]. It remains unresolved if incidental LRP represents preclinical PD or even preclinical DLB [48, 135], but this seems likely based on intermediate values between normal with no LRP and PD for a number of quantitative parameters [37]. The clinical significance of incidental LRP has been addressed in several prospective studies, which suggest that it is associated with several features that are increasingly recognized as early non-motor manifestations, including rapid eye movement sleep behavior disorder [16, 168], anosmia or hyposmia [139] and evidence of autonomic dysfunction, such as constipation [2]. The environmental risk factors for incidental LRP appear to be similar to that of PD [49], but this is an area that requires further investigation. Little is known about genetic risk factors for incidental LRP, but as in PD [86, 171], apolipoprotein E does not seem to be a risk factor [141]. Nothing is known about the influence of other genes implicated in genomic association studies of PD [114].

LRP are detected in a number of movement disorders, such as adult polyglucosan disease with DOPA-responsive tremor [160], some patients with DOPA-responsive dystonia [125] and in elderly individuals with essential tremor [103, 104]. Given the presence of not only LRP, but also neuronal loss in these disorders, it could be argued that LRP in these disorders plays an essential role in the disease process. Alternatively, they may merely have concurrent PD along with their primary disease process.

Incidental LRP are also detected in a range of neurodegenerative disorders that have no clear relevance to α-synucleinopathies, including the tauopathies progressive

supranuclear palsy [166], corticobasal degeneration [50] and Pick's disease [138]. The density and distribution of LRP in these conditions bears striking resemblance to that seen in incidental LRP. Moreover, the absence of any distinguishing features for cases with and without LRP suggests that they are indeed coincidental [166]. LRP are uncommon in familial tauopathies [188] and have not been detected in a series of 25 frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) cases due to mutations in the tau gene (*MAPT*) (unpublished, DWD). Less is known about the frequency of LRP in frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) or FUS pathologies. There are isolated reports of LRP in patients with FTLD-TDP due to mutations in the gene encoding progranulin (*GRN*) [84, 92, 112], and in at least some of the patients the clinical syndrome had features that were suggestive of DLB [84]. In a series of 199 cases of FTLD-TDP (71 ± 1 years of age at death; 101 men and 98 women), 13 (6.5%) had LRP with routine histologic methods (unpublished, DWD), clearly below a threshold where one would consider LRP to be a critical component of the disease process. Further studies of the range of disorders in which LRP are found are warranted to determine which neurodegenerative features might favor or protect from coincidental LRP.

Multiple system atrophy

Multiple system atrophy is a sporadic, adult onset, progressive neurodegenerative disease in which it has been recognized for some time that patients present with the variable features of parkinsonism, cerebellar ataxia, autonomic dysfunction and pyramidal signs [62]. Historically, three disorders were recognized—patients with predominantly cerebellar symptoms considered to be olivopontocerebellar atrophy (OPCA) [32]; patients with a parkinsonian disorder considered to be striatonigral degeneration (SND) [3]; and patients with primarily an autonomic dysfunction considered to be Shy–Drager syndrome (SDS) [149]. The realization in 1969 that these clinical features could occur together led to the recognition that this represented one disease and the term MSA was introduced [63]. The subsequent discovery of a common pathological hallmark (Figs. 1b, 4), the argyrophilic oligodendroglial Papp-Lantos body or glial cytoplasmic inclusion (GCI), in all clinical subtypes of the disease confirmed that they represent a single entity [75, 132]. Additional infrequent rod-shaped intranuclear oligodendroglia inclusions (Fig. 4), neuronal cytoplasmic inclusions (NCIs), fine thread-like neuronal intranuclear inclusions (Fig. 4b) and inclusions in neuronal processes were also observed [82, 100, 121, 133, 189]. The principal protein component of these glial and neuronal inclusions is now recognized as post-translationally modified, fibrillar α-synuclein, thus defining MSA as a member of the group of α-synucleinopathies [8, 42, 54, 55, 109, 154, 161, 175]. Although no coding mutations have been identified in the gene encoding α-synuclein (*SNCA*), recent studies have demonstrated single nucleotide polymorphisms in *SNCA* that confer an increased risk of developing MSA [4, 128, 140, 144]. These findings could not be replicated in a Korean cohort, suggesting that ethnicity may play an important role in genetic susceptibility to the disease [191]. A collaborative genome-wide association study using samples from multiple centers is currently underway and the results are awaited.

Clinical criteria for the diagnosis of probable and possible MSA during life have been agreed and include autonomic failure, parkinsonism that is poorly responsive to levodopa, a cerebellar syndrome and pyramidal signs [62]. In addition to the core features, there are other clinical observations that may aid in diagnosis. Patients with a predominantly cerebellar syndrome at the time of first evaluation are designated MSA-C, while those with a primarily parkinsonian disorder are recognized as MSA-P, although it is acknowledged that with disease progression the balance of the clinical features of movement disorder may alter [62]. In a study of European patients, 58% were classified as MSA-P and 42% had MSA-C. Interestingly, the clinical spectrum of MSA appears to show ethnic variation, with MSA-C being more common (approximately 84%) in Japanese patients than MSA-P [59, 130, 180, 186].

Epidemiological studies have shown an age adjusted prevalence in the UK of 4.4/100,000 [145]. The mean age at disease onset is 60 years, with a disease duration of 7–9 years [146]. While some studies indicate that males are more commonly affected than females (1.3 M:1F), others suggest that there is no difference between the sexes [181, 185]. MSA is considered to be a sporadic disorder; however, there are rare familial descriptions [69, 153], with pathological confirmation in a German pedigree with autosomal-dominant inheritance [184].

Pathological variability in MSA

The clinical involvement of olivopontocerebellar, striatonigral and autonomic systems in life has been recognized for some time [161]. Although patients may present with a predominantly parkinsonian or cerebellar syndrome, it is clear that at autopsy gliosis, α-synuclein pathology and neuronal loss are usually widely distributed and are not confined to either olivopontocerebellar or striatonigral regions (Table 5). In a study that included information from 203 pathologically confirmed cases of MSA, the severity of neuronal loss and gliosis in the putamen, globus pallidus and substantia nigra correlated with clinical akinesia while rigidity was correlated with pathological

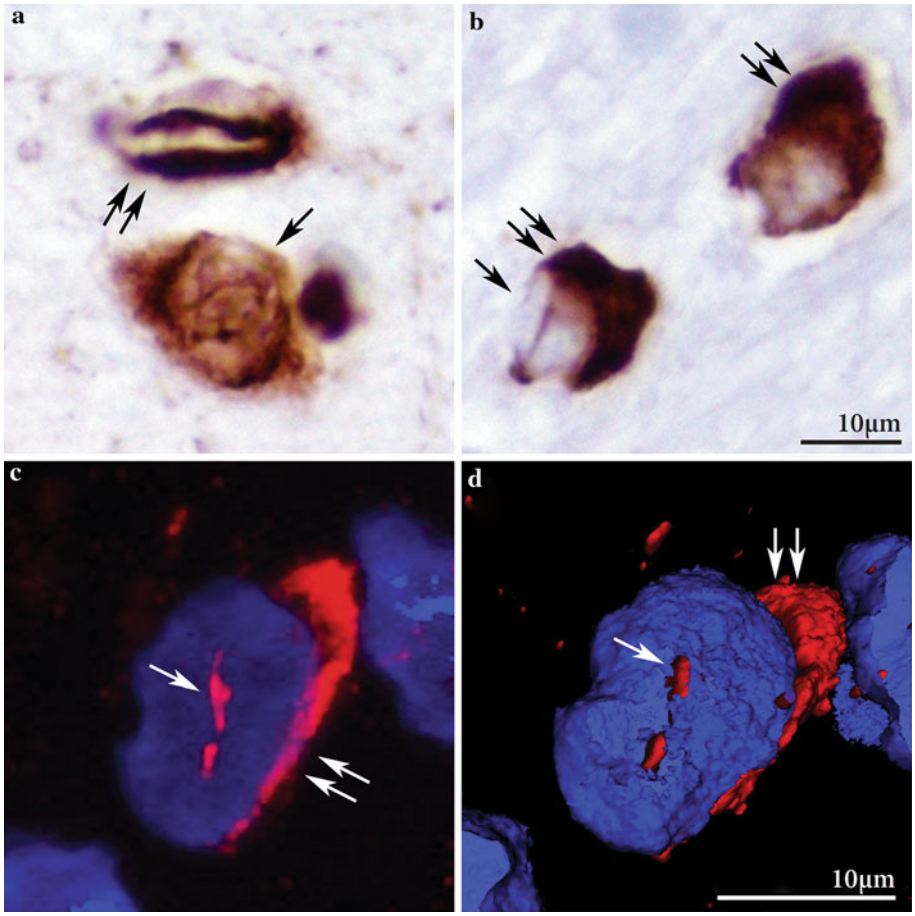

Fig. 4 Microscopic changes in multiple system atrophy. **a**, **b** High magnification image of 8-μm sections from the putamen immunoperoxidase stained for α-synuclein. α-Synuclein-immunoreactive GCIs can be seen in three oligodendrocytes (**a**, **b** *double arrows*) with one of these also having a fine intranuclear inclusion (**b** *arrow*). A small neuron contains a neuronal intranuclear inclusion (*arrow*) in addition to cytoplasmic immunoreactivity (**a**). **c** High magnification 20-μm sections from the putamen using immunofluorescence staining for α-synuclein (*red*) with a nuclear fluorescent counterstain (*blue*). An α-synuclein-immunoreactive GCI can be seen in the oligodendrocyte (*double arrow*) which also has an intranuclear inclusion (*arrow*). **d** 3D-rendition of α-synuclein immunofluorescent oligodendroglial cytoplasmic and nuclear inclusions observed in **c**. The cytoplasmic localization of a GCI is clearly seen (*double arrow*) in addition to the nuclear inclusion (*arrow*). Photomicrographs courtesy of Dr. Zeshan Ahmed, Queen Square Brain Bank

changes in the putamen (Fig. 5). Tremor could not be explained by pathological changes in any of the sites examined. Limb and gait ataxia were associated with neuronal loss in the inferior olives, pontine nuclei and also Purkinje cell depletion (Fig. 5) [181]. In the study of Ozawa et al., 80 cases had detailed clinical information available. In this group, cases with more severe bradykinesia in life had striatonigral degeneration while than those with olivopontocerebellar degeneration had more frequent cerebellar signs, supporting the idea that the clinical phenotype reflects the distribution of pathology in the basal ganglia and cerebellum. However, in a large neuropathological study of 100 cases from a UK brain bank, grading of neuronal loss showed that in 34% the striatonigral regions were most severely affected; in 17%, the olivopontocerebellar neuronal loss was the predominant finding, and these regions were equally affected in almost half of the cases [129]. In a comparable Japanese study, 40% of cases had greater olivopontocerebellar degeneration and 18% had greater striatonigral loss reflecting the previously reported difference in clinical presentation of the disease in this population [130, 176, 186]. It was also observed that relatively mild involvement of the substantia nigra was associated with parkinsonian features, although a greater degree of cerebellar pathology was required before cerebellar signs developed (Fig. 5) [129]. Those patients with less severe pathological changes in the putamen were found to have shown greater responsiveness to levodopa in life and this would be in keeping with previous evidence that neuronal densities in the putamen are greater in levodopa responsive MSA patients [44]. Thus, the generally poor response of patients with MSA to levodopa is likely to be due to extensive putaminal neuronal loss.

Table 5 Comparisons of neuropathological and clinical subtypes of MSA

Feature	Neuropathological subtype		References
	SND	OPCA	
Olivopontocerebellar predominant neuronal degeneration	–	17–40%	[129, 130]
Striatonigral predominant neuronal degeneration	18–34%	–	[129, 130]
Clinical correlate	Bradykinesia	Cerebellar syndrome	[129]
Insoluble α-synuclein	Present, no difference from OPCA	Present, no difference from SND	[38]
Density of neuronal α-synuclein inclusions	No difference from OPCA	No difference from SND	[38]

Feature	Clinical subtype		References
	MSA-P	MSA-C	
Percentage of MSA cases	16 (Japan)–58 (Europe)	42 (Europe)–84 (Japan)	[59, 130, 180, 186]
Clinical features at onset	Predominant parkinsonian syndrome	Predominant cerebellar syndrome	[62]
Cognitive impairment (overall 14–18%)	More frequent than in MSA-C	Less frequent than in MSA-P	[19, 83, 123]
Pyramidal signs (overall 54%)	Less frequent than in MSA-C	More frequent than in MSA-P	[59]
Autonomic clinical features	Present	Present	[127, 181]

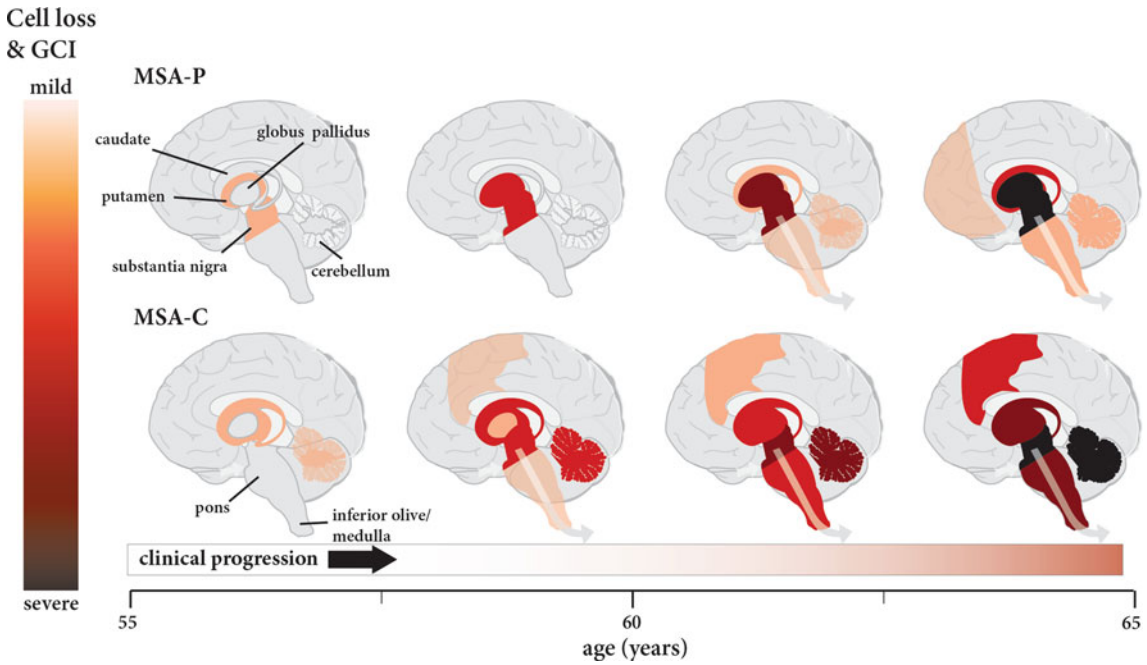

Fig. 5 Cartoon of the amounts and progression of pathology in the two major clinical phenotypes of MSA with oligodendroglial cytoplasmic inclusions

The relationship of GCIs to neurodegeneration in MSA has been the subject of some debate. In early studies, no relationship was found between the density of GCIs and the severity of neuronal loss [134]. More recent investigation of a large case series utilizing extensive sampling and semi-quantitative analysis of neuronal loss and GCI density has revealed a positive correlation between the density of GCIs and the degree of neuronal loss (Table 5), indicating that the accumulation of GCIs is likely to be an important factor in neurodegeneration in MSA [129]. In contrast, no difference in the density of neuronal cytoplasmic inclusions has been observed in the putamen, pontine nuclei and inferior olivary nuclei (Table 5). It is also of note that despite the loss of Purkinje cells in MSA, these cells have never been found to contain neuronal cytoplasmic inclusions, indicating that the severity of neuronal loss is not determined by inclusion formation alone [111, 129]. Biochemical studies have not revealed any differences in the abundance of detergent-

insoluble α-synuclein in cases between the different subtypes [38]. Although the pathological changes in MSA are usually found to be widespread at the time of autopsy, there have been a small number of reported cases in which neuronal loss is restricted to the substantia nigra and locus coeruleus with more extensive distribution of GCIs. These cases have been referred to as 'minimal change' MSA [74, 179]. A further case, in which the patient died following a short disease duration, had neuronal loss restricted to the pontine base, inferior olivary nucleus and Purkinje cells of the cerebellar vermis accompanied by much more widespread GCIs indicates that minimal change disease may also be restricted to the OPC regions [174].

Pyramidal signs occur more in MSA-C [62] and have been described in around 54% of patients [59]. The neuropathological correlate of these signs is proposed to be the presence of neuronal loss and GCIs in the motor cortex and pyramidal tracts (Fig. 5). GCIs are often abundant in the fifth and sixth laminae of the motor cortex and also the pyramidal tracts [134]. A case study of neuronal loss in the motor cortex originally indicated that there is preservation of Betz cells with the loss of small and medium-sized neurons in the deeper cortical laminae, which could be consistent with the loss of small myelinated axons in the corticospinal tracts in the spinal cord previously described [152, 173]. Subsequently, a more extensive study has demonstrated degeneration of Betz cells in the motor cortex in addition to myelin pallor and loss of small myelinated fibers in the pyramidal tracts in the spinal cord [165]. Clinicopathological correlation indicates that extensor plantar responses and hyperreflexia are both associated with abnormality of the pyramidal tracts reflected by myelin pallor [181].

The prominent clinical features of autonomic failure in MSA, which may precede the motor symptoms in both MSA subtypes are believed to be due to pathological changes in components of the autonomic system [127]. Neuropathological studies have provided evidence of degeneration of sympathetic neurons in the intermediolateral column of the thoracolumbar spinal cord, which is considered to contribute to orthostatic hypotension [9, 181]. In a clinicopathological analysis, autonomic features of syncope and urinary incontinence were found to be associated with such neuronal loss [181]. Disordered bladder, rectal, and sexual function in MSA have been associated with cell loss in parasympathetic preganglionic nuclei in Onuf's nucleus and in the inferior intermediolateral nucleus of the sacral spinal cord [87]. There is also thought to be a supraspinal component of autonomic failure as neuronal loss has been reported in a number of brainstem and hypothalamic nuclei, including the dorsal motor nucleus of the vagus [13, 157], the catecholaminergic neurons of ventrolateral medulla [14], serotonergic raphe nuclei [12], the Edinger–Westphal nucleus, the noradrenergic locus coeruleus [181] and the posterior hypothalamus [113, 149]. Most importantly, large numbers of GCIs can be found in the brainstem pontomedullary reticular formation, which is involved in cardiac regulation and the control of both respiration and micturition in addition to chemo- and baro-reception, thus providing a pathological basis for impaired visceral function [134]. Neuronal loss in the ventrolateral nucleus ambiguus, a source of cardiac vagal innervation, is likely to contribute to cardiovagal failure in MSA [13].

Cognitive impairment has not been widely recognized as a feature of MSA and until recently would have been regarded as a reason to reconsider the diagnosis [62, 178]. On the other hand, in studies with neuropathological ascertainment of MSA, cognitive impairment has been recorded in 14–18% of cases [19, 123]. Furthermore, cognitive impairment, consisting of visuospatial and constructional dysfunction, impairment of verbal fluency, dysexecutive syndrome and depression has been described to be more severe and widespread in patients with MSA-P than in patients with MSA-C [83]. The neuropathological basis of cognitive impairment in MSA has not been examined in detail. GCIs may be found in the neocortex and underlying white matter, most frequently in motor regions [134]. As described above, there may also be neuronal loss in the motor cortex. Macroscopic cortical atrophy is not commonly seen in MSA, but there are descriptions of rare cases of long disease duration in which there is significant ventricular dilatation with frontal and temporal atrophy [190]. The presence of frontal atrophy is documented by imaging studies in MSA in vivo [27]. Furthermore, SPECT studies have shown that the neuropsychological impairment in patients with MSA-P significantly correlates with a decrease in prefrontal perfusion, supporting the notion that frontal lobe involvement is responsible for cognitive dysfunction in MSA patients [83]. Neuronal α-synuclein pathology may also be found in the hippocampal formation and amygdala [7]. The relative contribution of cortical and subcortical pathological changes to cognitive impairment in MSA remains to be elucidated.

Other synucleinopathies

α-Synuclein is detected in a range of other disorders including disorders with axonal spheroids. In addition, α-synuclein immunoreactivity also occurs in neurofibrillary tangles and dystrophic neurites of neuritic plaques.

α-Synuclein in neuroaxonal dystrophies

Abnormal α-synuclein deposition has been demonstrated with immunohistochemistry in a range of disorders

associated with neuroaxonal dystrophy, including age-related axonal dystrophy in the pallidonigral distribution and axonal dystrophy associated with traumatic brain injury [120]. It is also detected in axonal pathology associated with motor neuron disease [41], as well as spheroids in neurodegeneration with brain iron accumulation type 1 due to mutations in pantothenate kinase type 2 (*PANK2*, Table 3) [56, 119, 159, 172] and in infantile neuroaxonal dystrophy due to mutations in the phospholipase A2, group VI (*PLA2G6*, Table 3) [131]. In some of these cases, spheroids are accompanied by LRP (Fig. 6d) [159], while in others the abnormal α-synuclein is limited to axonal spheroids. α-Synuclein does not appear to be a component of axonal dystrophy associated with diffuse leukoencephalopathy with spheroids/pigmented orthochromatic leukodystrophy [182]. Given that α-synuclein is actively transported in axons [80, 99, 169] and accumulates at sites of axonal injury [80], the presence of α-synuclein in neuroaxonal dystrophies is perhaps not too surprising. It is worth noting that many Lewy neurites, which are one of the histopathologic hallmarks of LRP, also appear to be derived from axons (Fig. 6a–c), in that immunoelectron microscopic studies show partial investment of Lewy neurites with myelin [39].

α-Synuclein-associated with Alzheimer type tau

Not including cases with combined AD and LRP (see above), α-synuclein is also detected in a subset of neurofibrillary tangles and of dystrophic neurites in senile plaques. At the ultrastructural level, these lesions show two distinct types of filaments—tau paired helical filaments and α-synuclein straight fibrils [53, 164]. Neuronal lesions with co-deposition of tau and α-synuclein are particularly common in the olfactory bulb and in the amygdala, which are some of the most severely affected anatomical structures in both LRP and AD. As a rule, when α-synuclein is detected in neurofibrillary tangles and dystrophic neurites within neuritic plaques in AD, it warrants investigation for other evidence of LRP pathology in other brain regions, although some will only have limbic lobe pathology.

If LRP is not increased in frequency in disorders, such as progressive supranuclear and FTDP-17 due to *MAPT* mutations (see above), most of which are 4R tauopathies [21], and is increased in AD pathologic tau which contains both 3R and 4R tau [150], perhaps the AD nature of tau favors α-synuclein co-deposition. In support of this hypothesis, other disorders associated with AD tau, including diffuse neurofibrillary tangles with calcification [89], Guam Parkinson dementia complex [22], Niemann–Pick type C [158] and some cases of Gerstmann–Straussler–Scheinker syndrome [60] have all been reported to have LRP as a concomitant finding in some cases, especially in limbic structures such as the amygdala [23, 45, 73, 142, 147, 187]. It remains to be determined if dementia pugilistica, also known as chronic traumatic encephalopathy, which has AD tau [107, 143], also has an increased frequency of LRP.

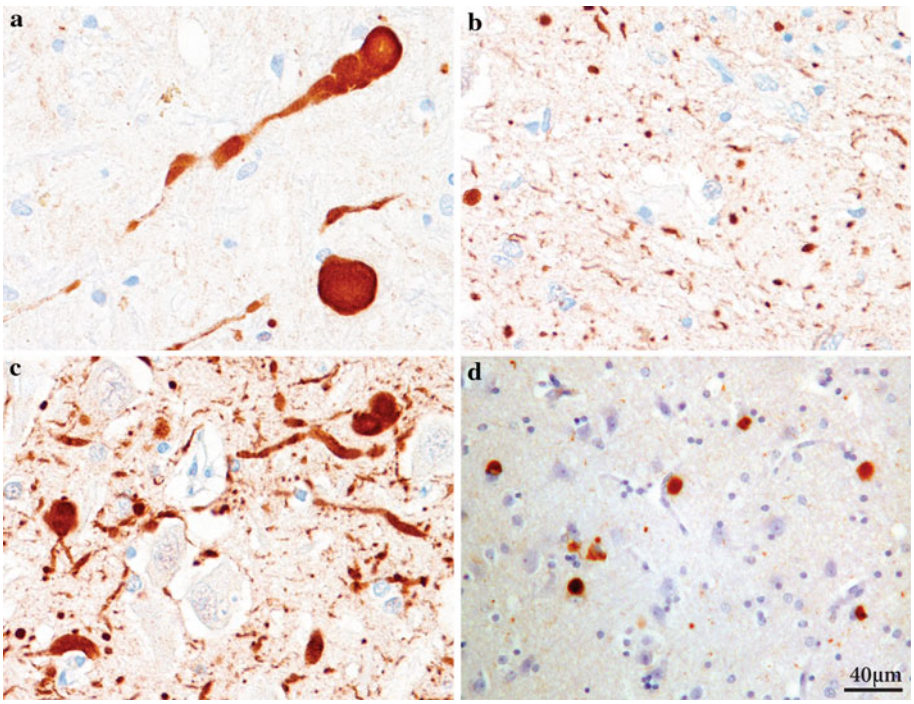

Fig. 6 α-Synuclein pathology in other disorders. Axonal spheroids (**a**), abnormal α-synuclein aggregates in myelinated axons (**b**) and dystrophic axons and neurites (**c**) in Lewy body disease. Scale equivalent to **d**. **d** Frequent α-synuclein-immunoreactive cortical Lewy bodies in the temporal neocortex of a 36-year-old woman with compound heterozygous mutation of the PLA2G6 gene

Conclusions

The abnormal deposition of α-synuclein occurs in both neurons and glia in a variety of clinical syndromes, often as incidental findings. For three main syndromes, the deposition of the protein is the dominant pathology, although the rate and location of deposition differs between patients. Clinical acumen and modern cluster analyses have shown that this variation in α-synuclein deposition identifies different clinical phenotypes within the three main synucleinopathy syndromes. For some phenotypes, such information has helped to elucidate the mechanisms behind more limited responses to current dopamine-replacement therapies. Although there has been considerable headway in relation to understanding the clinical features of these syndromes, further collaborative studies in which large numbers of clinically well-documented cases with neuropathological confirmation of their diagnosis are still required to firmly establish pathological correlations to clinical phenotype. Such information is essential to identify underlying initiating and risk factors, and to develop target-specific treatments for patients with differing forms of synucleinopathy syndromes.

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