The spectrum of clinical features seen with alpha synuclein pathology

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ABSTRACT

It has been recognised for many years that a number of chronic neurodegenerative diseases of the CNS are characterised by the development of intracellular inclusion bodies, but it is only relatively recently that the core proteins defining these pathologies have been defined. One such protein is alpha synuclein, that was found to be the main component of Lewy bodies in the late 1990s, and this discovery reinforced the emerging view that alpha synuclein was intimately linked to diseases characterised by this type of pathology - namely Parkinson’s disease (PD) and Lewy body dementia (DLB). Furthermore at around this time this same protein was also found within the glial inclusion bodies of patients dying with Multiple System atrophy (MSA). These three disorders constitute the majority of patients with an ‘alpha synucleinopathy’, although there are a number of rarer conditions that can also cause this pathology including inherited metabolic disorders such as Gaucher’s Disease (GD). In this review we will concentrate on PD, the commonest alpha synucleinopathy, and its associated dementia (PDD), as well as discussing DLB and MSA and will highlight how the clinical features of these conditions vary as a function of pathology.
**INTRODUCTION**

When James Parkinson described the clinical cases that were later to take his name in 1817,(1) he had no idea that the condition would still be the subject of intense debate nearly 200 years later - not least in terms of what defines the condition clinically. The early recognition of the motor features of Parkinson’s disease (PD) led to these being seen as the dominant aspect of the condition, even though early on many clinicians recognised that there were non-motor aspects to the disease including the development of a dementia in some patients (e.g William Gowers). Even today the diagnosis of Parkinson’s disease is based on the presence of cardinal motor features in the absence of other aetiological conditions or agents such as dopamine blocking drugs (see Table 1 for the UK Parkinson’s Disease Brain Bank diagnostic criteria(2)). These motor features include the classical triad of bradykinesia, a resting pill-rolling tremor, and rigidity typically in association with hypomimia, hypophonia, micrographia and postural instability. However it is now recognised that not all patients exhibit these features in equal measure and that many non-motor features occur in PD from the time of diagnosis. Indeed there is now great interest in the idea that the non-motor features of PD may even precede its diagnosis, constituting prodromal or premotor PD. These premotor features include problems with olfaction, constipation, mood and sleep and following the clinical diagnosis of PD they can become more prominent and debilitating and may be aggravated by the use of the dopaminergic drugs used to treat the motor aspects of PD. Cognitive problems and dementia also commonly develop in PD, affecting almost 50% by 10 years from diagnosis.(3) However, in some individuals with an alpha synucleinopathy, significant cognitive problems precede the onset of parkinsonian motor symptoms, and these cases are clinically classified with a diagnosis of Dementia with Lewy Bodies. There is clearly a major degree of overlap between these two conditions both clinically and pathologically, but at present, the clinical distinction rests on the time interval between the onset of motor symptoms and dementia, with a minimum one year interval being required for a diagnosis of PD as opposed to DLB.(4) Multiple System Atrophy (MSA) is the rarest of the three major alpha synucleinopathies and differs significantly from PD and DLB in terms of its clinical presentation and its more aggressive course, reflecting differences in the underlying neuroanatomical pathways involved.

In this review we will first discuss PD in terms of its prodromal state, and go on to discuss the natural history of PD following its diagnosis, its typical clinical manifestations, and complications of its treatment. We will then highlight the differences in clinical presentation in other alpha-synucleinopathies, including DLB and MSA. We will conclude by discussing whether diagnosing patients with specific clinical conditions is useful, or whether we should move more towards classifying parkinsonian syndromes with a common pathological basis, to facilitate a combined approach to developing new therapies directed against alpha synuclein aggregates.

**PARKINSON’S DISEASE**

**Prodromal PD**

The discovery that alpha synuclein was the major protein in Lewy bodies in 1997(5) led to a re-evaluation of the pathology of PD at the end of the last century using immunohistochemical staining against this protein. This was done most notably by Braak and colleagues and led to a new pathological staging system for PD, in which the early stages were characterised by non-nigral pathology and the substantia nigra was affected only at stage 3. Stages 1 and 2 involved more caudal
brainstem nuclei including the dorsal vagal nucleus and the locus coerules as well as the olfactory bulb.\(^6\), \(^7\) If this proposed pathological staging of PD was correct, then this should have clinical correlations i.e. patients at the time of presentation with their motor symptoms should have a prior history of anosmia, gut disturbances and changes in lower brainstem functions such as gait, mood and sleep. Subsequently this has been shown to be true for the majority of patients,\(^8\) although in clinical practice these features are rarely volunteered by the patient who typically considers them irrelevant to their motor problems, and they often have to be specifically asked about. Thus in the patient presenting for the first time there is often a history of:

- A loss of the sense of smell for some years;
- A slowing up in walking;
- Constipation;
- Mild anxiety or depression (although the hypomimia of PD can be mistaken for depression);
- REM sleep behavioural disorder (RBD) in which patients act out their dreams.

While all of these symptoms can occur for a number of other reasons, their presence in a patient with subtle motor features of parkinsonism is very suggestive of a diagnosis of PD, although can also be seen in other alpha synucleinopathies.

This recognition of this ‘premotor’ state of PD has had two major consequences to the field, in addition to helping diagnostically at the initial consultation.

Firstly it has led to clinical studies searching for even earlier pathology in structures projecting into the dorsal vagal nucleus, namely in the gut. This has revealed that the alpha synuclein pathology is present in the gastrointestinal tract not only in patients with established PD,\(^9\), \(^10\) but in some cases in advance of the motor presentation.\(^11\) This supports the concept that PD has non-CNS pathology, and the disease may even begin outside the brain. More recently some of these claims of early pathology in the gut in PD have been challenged based on questions of antibody specificity\(^12\), and thus whether this truly is the site of the earliest problems in PD is debated.\(^13\)

The second major consequence is that programmes of research have been set up to either screen aging populations to identify individuals at risk of developing PD based on olfaction tests, sleep assessments +/- dopamine scans,\(^14\), \(^15\) or alternatively to follow up individuals thought to be at high risk of developing an alpha synucleinopathy, for example those with REM Sleep Behaviour Disorder.\(^16\), \(^17\) The advantage of the screening approach is the capacity to pick up individuals at the earliest possible time in their disease course, which would be optimal for delivery of any disease modifying therapies, although in the absence of such an agent the approach has less merit. The second approach of following high risk groups offers the same advantage but also provides more evidence that the proposed pathological staging of PD is clinically relevant. In this latter respect, several studies have now shown that many patients with late onset RBD go on to develop some form of alpha-synucleinopathy within a number of years of developing their sleep disorder.\(^16\), \(^18\)\^-\(^20\) However, in some reported cases, very long intervals have been reported between the onset of the RBD and being diagnosed with PD and it may be that some of these patients have co-incidental RBD rather than a prodromal PD state.\(^19\)

While this whole approach has changed our understanding of alpha synucleinopathies, it has always been the case that the more eloquent patient can describe many changes that they noticed years
ahead of the diagnosis finally being made. These changes typically involve subtle motor deficits, such as the wearing out of one shoe more than the other, or an inability to accurately complete some complex motor acts in sport for example throwing the ball up to serve in tennis. Thus while we have recently concentrated on the non-motor aspects of prodromal PD, it may be the case that subtle motor deficits begin at a similar time.

**Clinical presentation of PD**

Whilst the motor features of PD already described are the best recognised aspects of the condition, patients often have a range of non-motor symptoms in addition to those that characterise the prodromal phase. These include insomnia, fatigue, daytime somnolence, pain, urinary symptoms, sweating, mood and cognitive deficits. Some of these are in part secondary to the underlying motor problems, for example, the inability to move quickly and fluently will make one more tired, and difficulty moving at night will wake patients up and this can lead to the daytime symptoms of sleepiness, fatigue and a loss of motivation. Furthermore the condition is very heterogeneous with patients presenting with different combinations of motor and non-motor features, which makes generalisations about this condition difficult.

Nevertheless the non-motor features are now considered to be a universal feature of PD at diagnosis, although how they evolve over time varies. This may reflect variation in the extent of alpha synuclein pathology in different cases, but also the extent of other pathological changes including Alzheimer’s type changes which are thought to contribute to the cognitive problems in PD.(21) However not all this variability in non-motor features relates directly to underlying neurodegenerative pathology: non motor symptoms are exacerbated by the drugs used to treat PD, for example dopamine agonists can cause daytime somnolence and levodopa can affect cognition; in addition some of the early executive and working memory deficits in PD are due to compensatory upregulation of dopamine pathways in frontal cortical areas,(22) and modulated by genetically determined variation in COMT enzyme activity, as well as dopaminergic medication.(23) As such some of these deficits can improve over time as pathology progresses into the frontal cortex, or medications are altered.

The diagnosis of PD relies on the recognition of the cardinal motor features (table 1) but in some cases the early motor signs can be difficult to distinguish from other conditions such as Essential (ET) or Dystonic Tremor (DT), which can have a degree of cogwheeling secondary to tremor which can be mistaken for rigidity; MSA and Progressive Supranuclear Palsy- Parkinsonism (PSP-P) which can present with motor features of parkinsonism. In the case of a tremor-dominant presentation, dopamine transporter SPECT scanning can be very helpful to distinguish PD (with striatal presynaptic dopamine deficiency) from ET and DT (with preserved presynaptic dopamine terminals).(24) Such scans cannot distinguish between PD and other neurodegenerative causes of parkinsonism such as MSA or PSP-P however, but clinical clues to the diagnosis of MSA and PSP-P include their failure to respond to dopaminergic therapies, and the involvement of other systems in addition to the extrapyramidal motor system at an early stage, especially in MSA. In particular, the early involvement in the latter of the autonomic nervous system results in marked postural hypotension, erectile dysfunction and sphincter problems that can all occur in PD but typically much later in the disease course. Nevertheless this condition is still easy to misdiagnose, as longitudinal studies have demonstrated when the patients come to post mortem.(25)
The other mimic that can sometimes be difficult to distinguish from PD is the elderly patient with a history of hypertension and diabetes and extensive cerebrovascular small vessel disease. In these cases the patient has a parkinsonian gait, but little in the way of neurological signs when examined on the couch. These patients are often described as having lower body parkinsonism or gait ignition problems. In these cases, an MRI scan can be helpful, although most elderly patients will have some evidence of small vessel disease on such a scan, and thus the diagnosis is based on interpretation of the degree of such changes in the context of the level of clinical disability. Even if a vascular cause for parkinsonism is suspected, a trial of levodopa is generally worthwhile in these cases in case there is a degree of underlying dopa-responsive PD.

Variability in the natural history of PD

The clinical course that patients follow from the time of diagnosis is very variable, as has been revealed in the two major epidemiological studies we have conducted this century in Cambridgeshire in the UK. These studies have collected community-based population-representative cohorts of newly diagnosed incident PD patients using well defined geographical, temporal and diagnostic criteria. The first of these – the CamPaIGN study- began in 2000 (26) and surviving patients from this cohort are still being followed up, (3) now up to 15 years from diagnosis. We are now validating the findings of this study in a second cohort (PICNICS) recruited at a later date in the same geographical region using similar techniques. A number of other longitudinal studies have now also been undertaken to look at the natural history of PD, (27-31) but it is arguably only those that derive incident PD cases from the community (27-29) which accurately record how the disease truly behaves in the population. Hospital-based cohorts are subject to bias as they recruit more able patients, who tend to be younger, and this also means that such cohorts are enriched for the rarer monogenic forms of the condition.

Through the long term follow up of the cohort recruited to the CamPaIGN study we have described the following main findings:(3, 32-34)

- The average age of PD diagnosis is around 68 years of age;
- PD does not adversely affect life expectancy as the mortality rate in this cohort was similar to that in the local age and sex matched population without PD;
- Cause of death as recorded on death certificates is not directly attributable to PD in the majority;
- The cumulative probability of developing PDD at 10 years into the illness is 46%, with the earliest cognitive deficits predicting its onset being problems with a more posterior cortical basis, including semantic fluency (generating names of animals in 90 seconds) and visuospatial function (copying an interlocking pentagons figure); conversely frontostriatally-based executive cognitive deficits do not predict an early dementia and can improve in some cases as the disease progresses;
- 68% of patients have developed postural instability at 10 years (Hoehn & Yahr stage 3), which is a key milestone in this condition, associated with a significant impact on quality of life;
- A quarter of patients are doing well at 10 years from diagnosis, surviving with no major cognitive or balance problems.
Differences in rate of progression to key milestones such as postural instability and PDD is presumed to reflect differences in the speed at which alpha-synuclein related pathology spreads from relatively localised nigrostriatal involvement, when the L-dopa responsive motor symptoms predominate, to widespread pathology throughout the cortex, when significant gait and balance problems and dementia occur (Figure 1). The obvious question which follows is why the time interval from diagnosis to these complications varies by so many years between individuals, i.e. what determines whether you do well or badly with PD? The most obvious factor is age, with older patients doing less well than younger ones (which was not accounted for by monogenic forms of PD in the CamPaIGN cohort)(3), with the exception of L-dopa induced dyskinesia which tends to affect younger patients more than older ones (Comparing clinical features of young onset, middle onset and late onset Parkinson’s disease.)(35) Other age-related comorbidities were also found to contribute to outcomes in our cohort,(3) but more recently genetic variants have been recognised to contribute to prognosis in PD (Figure 1).

The commonest genetic factor associated with developing PD is mutations within the GBA, the gene which encodes the enzyme glucocerebrosidase, which in their homozygous or compound heterozygous mutant form cause Gaucher’s disease. However heterozygotes are predisposed to PD that typically presents slightly earlier in life and follows a more aggressive course than idiopathic PD.(36) In our own study patients in possession of such a mutation had a five times greater risk of dementia over a median follow-up period of 6 years from diagnosis.(37) The mechanism by which defects in this gene cause disease is unclear as they do not seem to simply relate to decreased enzyme activity but rather to abnormalities in lysosomal function. This may involve a positive feedback loop occurring once the disease starts, such that intracellular alpha synuclein aggregation compromises GBA activity and lysosomal function which in turn causes worsening alpha synuclein aggregation and so on.(38)

Another major genetic factor implicated in disease progression in PD is MAPT (microtubule-associated protein tau) haplotype, with the H1 haplotype being associated with an increased risk of developing the disease, and an earlier onset of PDD.(32, 39) The underlying mechanism is unclear, but possession of the H1 MAPT haplotype in the context of PD does seem to alter the ratio of 3 to 4 repeat tau which may be significant, given that tau pathology is reported to contribute to the dementia of PD in some cases.(21) Furthermore tau aggregation may promote aggregation of alpha synuclein,(40) with hybrid oligomers recently being reported in PD brain.(41) Finally the role of variants in Apolipoprotein E (ApoE) in the development of PD and the dementia associated with it have been debated for some time,(42) but recent studies in large clinical cohorts indicate that dementia is significantly more common in PD cases carrying the APOE-ε4 allele.(43) While it has been suggested that this reflects concurrent Alzheimer’s disease pathology in these cases, APOE-ε4 carrier status is also associated with dementia in pathologically ‘pure’ alpha synucleinopathies.(44) As larger clinical datasets become available for genetic analysis in the future, additional genetic factors may be identified which could help explain why patients follow different clinical courses, and in particular why some develop major untreatable complications such PDD and balance problems at an early stage.

Motor progression in PD
The motor course of PD often follows a predictable course with patients initially responding well to dopaminergic medication for a number of years. The first sign that the treatment is starting to fail is that patients report that the effect of their L-dopa does not last until their next dose – the so-called ‘wearing off’ phenomenon. This can be managed by adding in a dopamine agonist, increasing the frequency of L-dopa doses and/or adding in monoamine oxidase inhibitors (MAOIs) or catechol-o-methyltransferase (COMT) inhibitors, but this subsequently gives way to more marked ‘on-off’ motor fluctuations with some doses of medication not producing any benefit. Patients also begin to experience involuntary movement when on their L-dopa, so called L-dopa induced dyskinesias (LIDs). These are exacerbated by stress, infections or tiredness. Initially the patient is often oblivious to their existence, and they are noticed only by the spouse or carer, but ultimately they become more apparent to the patient. Whilst dyskinesias can be improved by reducing the dose of L-dopa, patients generally prefer to maintain their L-dopa dose in spite of these movements rather than reduce it and increase their time in an ‘off’ state, which most patients find to be one of the most frightening parts of their illness. The rate at which dyskinesias develop is dependent on the age of onset and the dose of L-dopa they are taking but most patients will have some LIDs by 10 years from diagnosis, with an estimated mean time to dyskinesia onset of 6.6 years in our own community-based cohort. They are initially managed by fractionating the L-dopa medication into more frequent doses, and introducing amantadine. As the dyskinesias become more troublesome, management options include the introduction of continuous dopaminergic therapies such as apomorphine or enteral DuoDopa pumps, or deep brain stimulation, typically to the subthalamic nucleus, which allows for significant reduction in L-dopa dosing.

In addition to these motor fluctuations, patients typically experience increasing problems with their gait in the later stages of their disease due to freezing of gait, balance problems, and postural hypotension related to autonomic disturbance as well as medication. Indeed clinically there seems to be a critical tipping point in patients when they develop a triad of problems with postural hypotension, freezing of gait and neuropsychiatric problems and at this stage it seems that the alpha synuclein pathology has spread to involve areas where dopaminergic drugs not only don’t help but can actually make things worse. Such a state is often the harbinger of the final stages of PD and the need to start planning long term care packages and nursing home placement.

**Neuropsychiatric features of PD**

The development of motor complications in treated PD is inevitable but the development of neuropsychiatric features is more variable, as we have already discussed with respect to PDD. The most common neuropsychiatric problems relate to mood disturbance, with depression affecting around 35% of PD patients. Whilst multiple aetiological factors including psychosocial factors related to receiving a diagnosis of PD clearly contribute, depression is thought to be an intrinsic feature of the condition related to disturbances of noradrenergic and dopaminergic transmission as well as Lewy body deposition in limbic structures. In some cases, depression in PD can be severe and resistant to treatment with conventional anti-depressant therapies, such that ECT is needed. However in most cases it is relatively mild, and can be difficult to diagnose, as it is not always clear whether symptoms such as lack of motivation, fatigue, poor concentration and sleep disturbance are direct manifestations of PD or reflect an associated depression. Anxiety may also affect up to a third of PD patients, either co-existing with depression or occurring independently. It is often seen...
in the context of tremor-dominant disease, and can also be particularly problematic during ‘off’ fluctuations. In contrast mania is rarely seen in PD.

With disease progression, other neuropsychiatric problems emerge and are often a harbinger of PDD. They are typically aggravated by the dopaminergic medication, and by the amantadine used to manage the LIDs. These problems initially take the form of visual phenomena, with the patient thinking they can see something out of the corner of their eye, although when they turn around to see what it is, it isn’t there. When present, it is easy to see how this can lead to a degree of paranoia, with patients experiencing a feeling that they are being spied on. In addition, they also start to experience hallucinations, typically in the visual domain. This involves seeing animate objects, often at times of low illumination and driven by misperception of real objects, such as complex patterns on carpets or objects sitting on top of cupboards. These creatures are initially recognised as not being real, but with time this insight is lost and visual hallucinations can take the form of grotesque shapes as well as people. These symptoms are often very distressing and can lead to significant behavioural problems which necessitate reducing their standard medication and/or introducing treatment with cholinesterase inhibitors or low dose quetiapine. In some patients these problems can develop into a whole delusional system, with patients thinking other people are living in the house and/or their spouse being an imposter (Capgras syndrome). Although the development of these features can be controlled pharmacologically in their early stages, they will tend to recur and progress and their presence typically suggests that the patient is beginning to develop PDD with accompanying cortical Lewy body pathology.

**Other non-motor complications in PD**

The other major developments in advancing PD involve problems with speech, swallowing, the gut and the autonomic nervous system. Speech becomes very quiet and slurred and in the advanced stages it can be very hard to understand what is being said, which can generate levels of frustration. It rarely responds to dopaminergic therapy or speech and language therapy at the more advanced stages, and may even be made worse by DBS. It can though occasionally respond to such interventions when given earlier in the condition. Swallowing problems can develop in later disease, which can be particularly problematic as patients with PD also tend to lose weight. In advanced cases enteral feeding through a PEG can be considered. However if swallowing difficulties are a major early feature in the disease then alternative diagnoses should be sought including other types of neurodegenerative disorders such as PSP.

The involvement of the autonomic nervous system in PD is variable but if it is an early major feature, then one should consider a diagnosis of MSA as discussed earlier. However most patients with PD will have some degree of autonomic involvement with the most common manifestation of this being postural hypotension, which again can be made worse by some of the medications used to treat the motor features of this condition. It can be subclinical in some cases, and in the absence of symptoms requires no treatment. However many patients experience dizziness and presyncopal symptoms on standing, walking or after a heavy meal, with or without ‘coathanger pain’ across the shoulders and neck. In more advanced stages it can cause blackouts (which can lead to other problems such as fractured hips and wrists or subdural haematomas) and needs to be treated with either fludrocortisone, domperidone, midodrine or a combination thereof in severe cases.
Other autonomic features in PD include problems with excessive sweating, bladder irritability and constipation. This latter feature is found in nearly all cases of PD, and as previously discussed, may even precede the development of motor features of the condition. The cause of the constipation in part relates to lack of mobility, but may also be due to alpha synuclein pathology in the enteric and autonomic nervous system. (51) It is treated, albeit often suboptimally, with standard laxatives.

Sleep problems are common in PD. In addition to the RBD which can occur from the prodromal phase, many patients have overnight motor problems which can lead to disturbed sleep including restless leg syndrome, and akinesia related to being “off”. In addition some patients experience vivid dreams with L-dopa medications and this too can disrupt sleep. Recent evidence also suggests there may be an intrinsic circadian rhythm abnormality from early stages of PD with altered cortisol and melatonin levels, as well as changes in peripheral clock gene expression. (52)

Finally patients can experience other problems such as difficulty with opening their eyes (eyelid opening apraxia), (53) cramps, pain and sensory symptoms many of which relate to the underlying motor state.

**Drug induced non motor complications in PD**

The use of dopaminergic medication is transformative for most patients with PD, but these agents are not without side effects as we have already discussed, including exacerbation of cognitive and neuropsychiatric symptoms, and postural hypotension, particularly in the later stages of the disease. However, dopamine agonists can also induce a number of other behavioural symptoms which have been increasingly recognised over the last 10-15 years. Impulse control disorders such as gambling, hypersexuality, compulsive shopping and compulsive eating, have been estimated to affect 14-25% of PD patients. (54) They can develop insidiously without being recognised as a problem by the patient, but can rapidly escalate with devastating consequences for the patient and their family with a complete breakdown in the home situation, which in turn can negatively impact of all aspects of the patients PD. Patients need to be specifically warned about these symptoms ahead of dopamine agonists being started, and they need to be actively screened for by the clinician. These problems are most commonly seen in younger male patients, often with a personal and/or family history of addictive behaviours such as alcoholism, drug abuse or gambling in the past and are thought to relate to overactivation of ventral striatal circuits by medication. (54) Other compulsive behaviours linked to dopaminergic medication use can also manifest in PD, including punding, which involves an intense pre-occupation with specific items leading to repetitive purposeless behaviours, for example collecting and sorting labels or buttons, or taking apart electrical items. (55) This tends to be seen in patients on high doses of levodopa medication who are often dyskinetic. Patients can also develop a problem with addiction to their dopaminergic medication (dopamine dysregulation syndrome) leading to them using excessive quantities with consequent side effects such as marked dyskinesia and problems with drug withdrawal. This is more common in younger, early onset patients on levodopa, and again there is often a history of addictive behaviours in the past. (54)

More commonly seen, but much less destructive, side effects with dopamine agonists include daytime somnolence which in some patients can lead to dramatic sleep attacks. This can have important implications for driving. In addition dopamine agonists can induce a degree of nausea along with a sense of the patient just feeling generally unwell. As such it is always critical in patients
with PD to take a detailed history so that one can ensure that some of their symptoms are not simply secondary to the medications being used.

**MULTIPLE SYSTEM ATROPHY (MSA)**

MSA is much rarer than PD with an estimated prevalence of 4.4 per 100,000 (PD is around 45 times more common). It also tends to present earlier than PD, with a mean age of onset of 54 years. The neuropathology includes cell loss and gliosis in nigrostriatal and olivopontocerebellar structures, and the pathological signature of this condition differs from the Lewy bodies of PD, and instead takes the form of glial cytoplasmic inclusions containing fibrillar alpha synuclein within oligodendrocytes. It presents with autonomic dysfunction along with parkinsonism and cerebellar dysfunction in varying combinations, and is clinically classified as being either mainly cerebellar in its presentation (MSA-C) or mainly parkinsonian (MSA-P). It typically follows a more aggressive course than PD with minimal response to dopaminergic medications. MRI can be helpful in some cases in distinguishing it from PD through the presence of a “hot cross bun” sign in the pons or T2 signal changes in the dorsolateral putamen.

MSA-C presents with a late onset cerebellar syndrome causing ataxia and dysarthria, with evidence of involvement of other systems such as autonomic disturbances (impotence, bladder dysfunction, postural hypotension), a degree of parkinsonism, and/or pyramidal signs such as brisk reflexes and spasticity in the limbs. In contrast MSA-P presents with a predominant parkinsonian syndrome which is often mistaken for PD, but with early prominent autonomic problems, a poor response to dopaminergic therapy, a gait that is often worse than anticipated from examination on the bed (because of the subtle cerebellar problems), a history of RBD and “sighing” with a degree of inspiratory stridor. These latter signs and symptoms need to specifically asked and looked for to aid the diagnosis. Significant cognitive dysfunction is not a prominent feature of MSA, but cognitive deficits can occur in this condition, predominantly in the frontal executive domain.

MSA evolves much more rapidly than PD, and patients soon become severely disabled with frequent falls, significant autonomic problems and difficulty with swallowing and speech. Their life expectancy is significantly shortened, with a median survival of about 6 years, but this is shorter in those with an older age at diagnosis. Sadly there are no major therapeutic interventions that improve this condition other than supportive therapies for helping with the bulbar and autonomic problems, as well as the use of CPAP and tracheostomy for the stridor. A minority of patients do experience a transient significant response to L-dopa medication, but in most cases these drugs make little impact and are best discontinued as they can aggravate other aspects of the condition. Other drugs that are commonly used in MSA are amantadine as this may help the ataxia to some extent, and medications such as fludrocortisone, midodrine and desmopressin to support the blood pressure. Anticholinergics can be used to treat urinary dysfunction but they may precipitate urinary retention, and catheterisation is often needed in the later stages.

**DEMENTIA WITH LEWY BODIES (DBL)**

DLB is a relatively common cause of dementia, estimated to account for up to 30% of dementia cases, and affecting up to 5% of those over the age of 75. Pathologically, it is defined by the presence of alpha synuclein containing Lewy bodies in the brain, but their distribution differs from that in PD, affecting the neocortex, limbic system and brainstem, in contrast to the nigrostriatal
and brainstem predominant pattern seen in early PD. However, as previously discussed, in the later stages of PD, cortical Lewy body pathology is common, along with development of a dementia, and it is debated whether LDB and PDD essentially represent the same pathological process separated by an arbitrary time factor or whether in fact they are truly different conditions. (63, 64) Recent genetic studies looking at variation within the alpha synuclein gene and risk of PD, PDD and DLB have indicated that these disorders have distinct genetic association profiles suggesting that they are in fact different disease processes with a common pathology. (Guella et al, 2015). Imaging studies have also indicated that DLB and PDD differ with respect to the cortical amyloid load, which is much greater in DLB and may be an important contributor to the early cognitive impairment in this condition.(65, 66)

Clinically, DLB is characterised by a progressive dementia with prominent visual hallucinations and delusions, and parkinsonism with bradykinesia and rigidity but typically minimal tremor. Marked cognitive fluctuations are a common feature of this condition, with episodes of confusion, excessive somnolence, and incoherent speech which can revert to a near normal state within hours. In all these respects, it can look very similar to PDD. The diagnostic distinction between the 2 conditions rests mainly in the difference in the temporal evolution of symptoms, with DLB being diagnosed in patients who develop a dementia within a year of developing parkinsonian features, while PDD defines people with pre-existing PD who then go on to develop a dementia at least 1 year after motor disease onset.(4)

Both DLB and PDD can be treated with cholinesterase inhibitors, which have some efficacy in the earlier stages of the dementia, and can be helpful for the hallucinations and behavioural symptoms as well as cognitive impairment.(67-69) However, eventually the disease fails to respond to any treatment and palliative care is all that can be offered.

INCIDENTAL LEWY BODY DISEASE AND OTHER CAUSES OF LEWY BODY PATHOLOGY

The finding of incidental Lewy body pathology in the elderly brain is not uncommon at post mortem. Clinicopathological studies have reported that such changes are not clearly associated with dementia risk or parkinsonian symptoms,(70, 71) but it is of course impossible to know whether in such cases the patients were in the early stages of PD or DLB which had not yet become clinically manifest. However, it is generally accepted that Lewy body deposition does seem to occur as part of the aging process, in much the same way as neurofibrillary tangles and amyloid plaques.

In addition there are a range of other conditions in which Lewy bodies can be seen. This includes rare metabolic storage disorders such as Gaucher’s disease, caused by mutations in the glucocerebrosidase gene and Sanfilippo syndrome, a storage disorder caused mutations in the alpha-N-acetylglucosaminidase (NAGLU) gene. Although rare, these cases have been instructive in better understanding the aetiology and possible pathogenic pathways leading to alpha synuclein aggregation and Lewy body pathology.(72, 73) In particular, the recognition of Lewy body pathology and parkinsonism in some Gaucher’s cases led to the finding that mutations in the glucocerebrosidase gene are the commonest genetic risk factor for PD,(74, 75) and opened up a new avenue of research into the role of lysosomal pathways in alpha synucleinopathies. (38)

CONCLUSION
The clinical features of alpha synucleinopathies have now been shown to be much more extensive than once thought. These conditions have a wide range of symptoms and signs that extend beyond motor deficits, even though these dominate the early clinical stages of most of these conditions. This growing understanding of the diversity of symptoms and signs in PD and related conditions has led to a re-evaluation of diagnostic criteria as well as ongoing debate as to when and where the disease begins. One of our major challenges for the future is to establish reliable clinical, laboratory and imaging markers to allow us to diagnose these conditions earlier, ahead of their characteristic motor presentation, as this opens up the possibility of trialling disease modifying therapies at a time when they have greatest chance of being most effective. Another consideration for the future is whether, given the clinical and pathological overlap between these conditions, we should move more towards classifying parkinsonian syndromes with a common pathological basis, rather than segregating these conditions. This would facilitate a combined approach across these disorders to new therapies targeted at alpha synuclein aggregates, such as novel immunotherapies.(76)

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**TABLE 1:** UKPDS Brain Bank criteria for the diagnosis of Parkinson’s disease. From Hughes et al, 1992.(2)

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<th>Step 1: Diagnosis of parkinsonian syndrome</th>
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<tbody>
<tr>
<td>- bradykinesia</td>
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<tr>
<td>- 1 or more of:</td>
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<tr>
<td>- rigidity</td>
</tr>
<tr>
<td>- rest tremor</td>
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<tr>
<td>- postural instability</td>
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<thead>
<tr>
<th>Step 2: Absence of the following exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>- repeated strokes with stepwise progression of parkinsonism</td>
</tr>
<tr>
<td>- history of repeated head injury</td>
</tr>
<tr>
<td>- history of definite encephalitis</td>
</tr>
<tr>
<td>- oculogyric crises</td>
</tr>
<tr>
<td>- neuroleptic treatment at symptom onset</td>
</tr>
<tr>
<td>- more than one affected relative</td>
</tr>
<tr>
<td>- sustained remission of symptoms</td>
</tr>
<tr>
<td>- strictly unilateral features after 3 years</td>
</tr>
<tr>
<td>- supranuclear gaze palsy</td>
</tr>
<tr>
<td>- cerebellar signs</td>
</tr>
<tr>
<td>- early severe autonomic involvement</td>
</tr>
<tr>
<td>- early severe dementia with disturbances of memory, language, and praxis</td>
</tr>
<tr>
<td>- Babinski sign</td>
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<tr>
<td>- presence of cerebral tumour or communicating hydrocephalus on brain imaging</td>
</tr>
<tr>
<td>- negative response to large doses of levodopa in absence of malabsorption</td>
</tr>
<tr>
<td>- MPTP exposure</td>
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<thead>
<tr>
<th>Step 3: Supportive criteria for Parkinson’s disease – 3 or more of the following required</th>
</tr>
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<tbody>
<tr>
<td>- unilateral onset</td>
</tr>
<tr>
<td>- rest tremor present</td>
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<tr>
<td>- progressive disorder</td>
</tr>
<tr>
<td>- persistent asymmetry affecting side of onset most</td>
</tr>
<tr>
<td>- excellent response (70-100%) to levodopa</td>
</tr>
<tr>
<td>- severe levodopa-induced chorea</td>
</tr>
<tr>
<td>- levodopa response for 5 years or more</td>
</tr>
<tr>
<td>- clinical course of 10 years or more</td>
</tr>
</tbody>
</table>
FIGURE LEGEND

Figure 1: Schematic representation of the clinical, pathological and genetic heterogeneity of PD. Patients are on a continuum between more benign forms of the disease, with slowly progressive L-dopa responsive symptoms and minimal cognitive problems, and malignant disease with early spread of alpha-synuclein related pathology to widespread brain regions, leading to the development of non L-dopa responsive motor symptoms and PDD at an early stage in their illness. The factors underlying this heterogeneity are not fully elucidated but include age at presentation, and genetic variation in the MAPT, GBA and APOE genes is associated with an earlier dementia.
REFERENCES


