

Parkinsonism at a Glance

Usually, it is easy to label a patient as Parkinsonian on observing them walk into the consulting room. The early symptoms of impaired dexterity and micrographia, rest tremor, difficulty with repetitive alternating movements such as beating eggs, cleaning teeth and wiping feet on the doormat, difficulty turning in bed, aches associated with muscular rigidity and dystonia, and a general history of slowing down are early pointers. Problems arise, however, when tremor is the only symptom or in classifying the syndrome in its early stages. Sometimes, one may have to wait until later in the disease course when symptoms and signs crystallise into a recognisable pattern. Although this waiting game may not alter ones initial pharmacotherapeutic management, early and accurate diagnosis is not just an academic exercise; the prognosis and problems arising in the different akinetic-rigid syndromes vary significantly and knowing what one is dealing with may aid:

- 1) Clinical management e.g. the identification of disease-specific complications at an earlier stage
- 2) Carer understanding and recognition of new problems (e.g. frontal behaviour)
- 3) Patient and carers to access specific support groups and possible additional services
- 4) Patients to plan their lives better
- 5) The planning of service provision (early referral to multi-disciplinary team members, social services, physical aids)
- 6) Participation in research at an earlier (and possibly more useful) stage in the disease (e.g. potential neuroprotective agents would need to be commenced as early as possible in the disease course).

Diagnosing the akinetic-rigid syndromes

If one was to generate an algorithm to illustrate the thought processes involved in the diagnosis of akinetic rigid (AR) syndromes, after the exclusion of secondary causes of Parkinsonism, i.e. those with an identifiable aetiology (see table 1 for overview and figure), idiopathic Parkinson's disease (IPD) would be the 'default' diagnosis. This makes sense because, although the other akinetic-rigid syndromes can present in exactly the same way, IPD is the most common and thus most likely diagnosis. One would then search for additional, 'atypical', features, which could change this default diagnosis to one of the other neurodegenerative akinetic-rigid syndromes. These atypical features are highlighted in figures 2-5 (MSA, PSP, CBD and DLB). All of these have a worse prognosis than IPD, tending to progress more rapidly. Life expectancy with MSA and PSP averages at around 6-7 years^{1,2} from symptom onset, although can be as little as 2 years.

Although 23% of IPD patients may never develop a tremor³, it is often the presenting complaint. The tremor-dominant form (TD) tends to have a better prognosis than the postural instability with dysfunctional gait (PIDG) form (more bradykinetic and rigid). Sometimes, in the perceived absence of bradykinesia and rigidity, it may be difficult to differentiate between an early presentation of IPD from other forms of tremor. In IPD, a resting tremor, which can be suppressed volitionally and is less prominent in posture and action, is typical. This, however, is not always the case. If treatment was indicated, one could prescribe a therapeutic trial of a dopaminergic agent. Unfortunately, parkinsonian tremor is much less responsive to treatment than bradykinesia and rigidity, so a negative result would not exclude the diagnosis. To assist the

diagnosis, one could arrange a 123I-FP-CIT SPECT scan (DaTscan™). This radioisotope-labelled ligand binds to the dopamine re-uptake transporter protein in the dopaminergic pre-synaptic terminals. So, a reduction in the binding may indicate loss of nigro-striatal neurones. In the case of an obviously abnormal result, with significant reduction in striatal binding, the diagnosis would be clear. The one study examining this found its sensitivity for Parkinsonism being between 95-97% and specificity for essential tremor being between 93-100%⁴. However, this study used clinically obvious cases with no pathological confirmation. Whether one can extrapolate to clinically uncertain cases remains to be seen. Also, it is currently a rather expensive test to use routinely. Longitudinal studies are currently in progress.

Dopa responsiveness

The current pharmacotherapeutic strategy of delaying the introduction of L-Dopa means that dopa-responsivity plays a lesser role in early diagnosis. The response to other treatments, such as dopamine agonists is helpful, although these are less effective at treating the motor symptoms than L-Dopa.

Dopa responsiveness is usually a reassuring sign, as one would expect this to occur in IPD. However, approximately 6% of IPD cases may show very little response⁵. Furthermore, patients with PSP or MSA may also respond to L-dopa^{1,5,6}, such that they may be misdiagnosed as IPD in the early stages, when atypical features are subtle or absent. In these cases, the response may be short lived, prompting a diagnostic review.

Diagnostic Criteria

The diagnosis of AR syndromes remains a clinical one, since there are no investigations that are sensitive and specific enough to differentiate between them. In order to consolidate the diagnosis one could employ the numerous research-based clinical diagnostic criteria. Notwithstanding their unwieldiness and debatable validity (they are based upon retrospective case-note reviews and post-mortem), a recent study confirmed that they did not improve upon the sensitivity and specificity of neurologists' own diagnostic acumen⁷.

In practice, one of the main difficulties arises in deciding upon the significance of possible atypical features. For example does a 68-year-old parkinsonian gentleman's urinary and erectile dysfunction mean he has MSA, or are they related to his prostatism and depression? What about his asymptomatic orthostatic hypotension - can it be related to the L-Dopa he is taking? And is the limitation of upgaze in an elderly lady with falls and Parkinsonism significant enough for a diagnosis of PSP? This is where criteria fall down, since they rely on subjective interpretations of objective features. This is where some of the more subtle features, not included in the diagnostic criteria may help with the diagnosis. For example dusky blue hands, nocturnal stridor, sighing, low amplitude myoclonic jerks (sometimes just affecting outstretched fingers when flicked by the examiner, termed polyminimyoclonus) or significantly reduced blink rate. However, this does not negate the usefulness of criteria; the key features contained within them are important to know⁸⁻¹¹ (included in figures) and it is the continuing refinement of such criteria through recognition of practical clinical difficulties that have helped to improve diagnostic accuracy.

References



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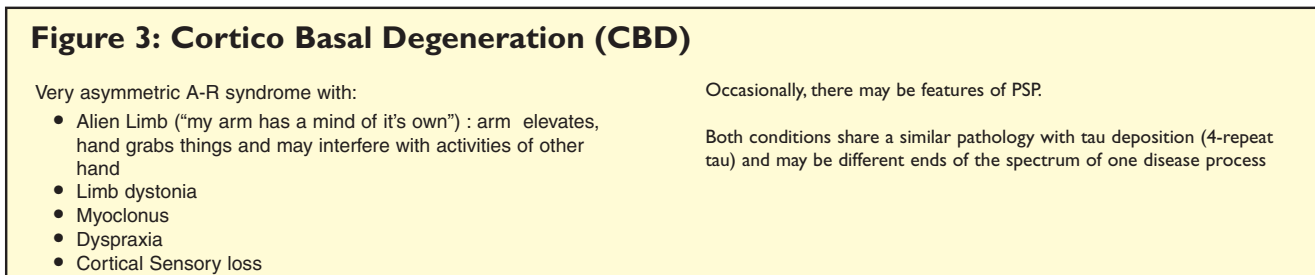
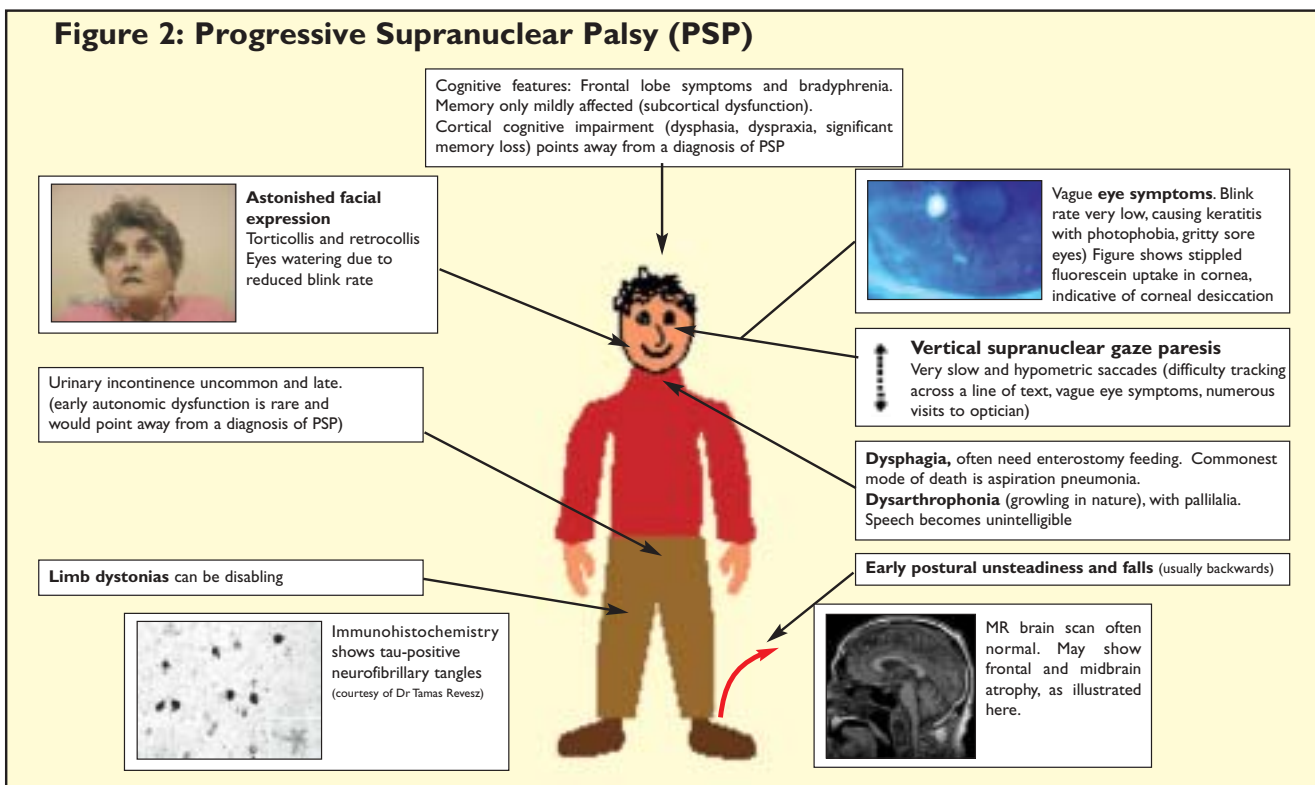


Table 1: Differential Diagnosis of Parkinsonism According to Identifiable Causes

Disease	Pathophysiology	Characteristic Clinical Features	Diagnosis
Brain Insult:			
Vascular Parkinsonism	Infarcts in the nigro-striatal pathways	Acute onset, stepwise progression Vascular risk factors Lower body Parkinsonism Low incidence of tremor Poor L-Dopa response Can mimic any A-R syndrome	Brain imaging (see fig 1) (Can be difficult though as there is a high incidence of vascular disease in patients with IPD)
Cerebral Tumour	Basal ganglia, midbrain infiltration/compression	Can mimic any A-R syndrome	Brain imaging
Hydrocephalus	unknown	Gait dyspraxia, dementia, urinary incontinence	Brain imaging
Pugilistic Parkinsonism	Repeated head trauma, possibly causing midbrain contusions/haemorrhage	Like IPD	Brain imaging shows evidence of previous midbrain haemorrhage.
Genetic Causes			
Wilson's disease	Hepatic copper transport protein deficiency; inability to excrete copper in bile, leading to copper deposition in basal ganglia.	Young onset Kaiser-Fleisher rings Psychiatric features Tongue tremor	δ Serum copper δ ²⁴ urine copper excretion αSerum Caeruloplasmin Liver biopsy
Parkin	Parkin mutation Autosomal recessive	Young onset Parkinson's disease (44% of <30 yr olds(12))	Genetic testing
Synuclein	/ – synuclein mutation Autosomal dominant	Very rare	Genetic testing
Westphal variant of Huntington's disease. Rarely: late onset	CAG repeat expansion in Huntingtin gene (function unknown) Autosomal Dominant	Young onset, Family History Late onset: may have myoclonus, dystonia, autonomic dysfunction ¹³	Genetic testing
Spinocerebellar ataxias, type 2, 3 and 6	SCA gene mutations	Parkinsonism and Cerebellar ataxia (may look like MSA-C) Family History	Genetic Testing
Infectious			
Whipples disease	The bacterium <i>Tropheryma whippleii</i>	Can present like PSP Other neurological features: neuropathy, myopathy, Orofacial myorhythmia Gastrointestinal disturbance	PAS +ve macrophages on duodenal biopsy PCR ofCSF
Post encephalitic	Unknown virus	Previous history of encephalitis Other movement disorders	Essentially clinical
CJD ¹⁴	Prion disease	Psychiatric features, myoclonus, supranuclear gaze paresis	Pulvinar high signal on MR scan with nvCJD 14-3-3 protein in CSF
Toxin			
Neuroleptics and other drugs	Dopamine receptor blockade	Like IPD	Withdraw drug if possible May take up to 15 months for Parkinsonism to resolve DaTscan to differentiate from IPD
Manganese Carbon Disulphide	Direct neurotoxic effects	Headaches, psychiatric disorders CS ₂ : also neuropathy	History of exposure
Carbon Monoxide	Ischaemic damage to basal ganglia	Like IPD, very severe, symmetrical	From clinical history ?gas fire at home. Imaging shows basal ganglia infarcts.

Figure 4: Multiple System Atrophy

MSA may take one of 2 forms, with increasing feature overlap as the disease progresses

MSA-C = Cerebellar Predominant

MSA-P = Parkinsonism Predominant

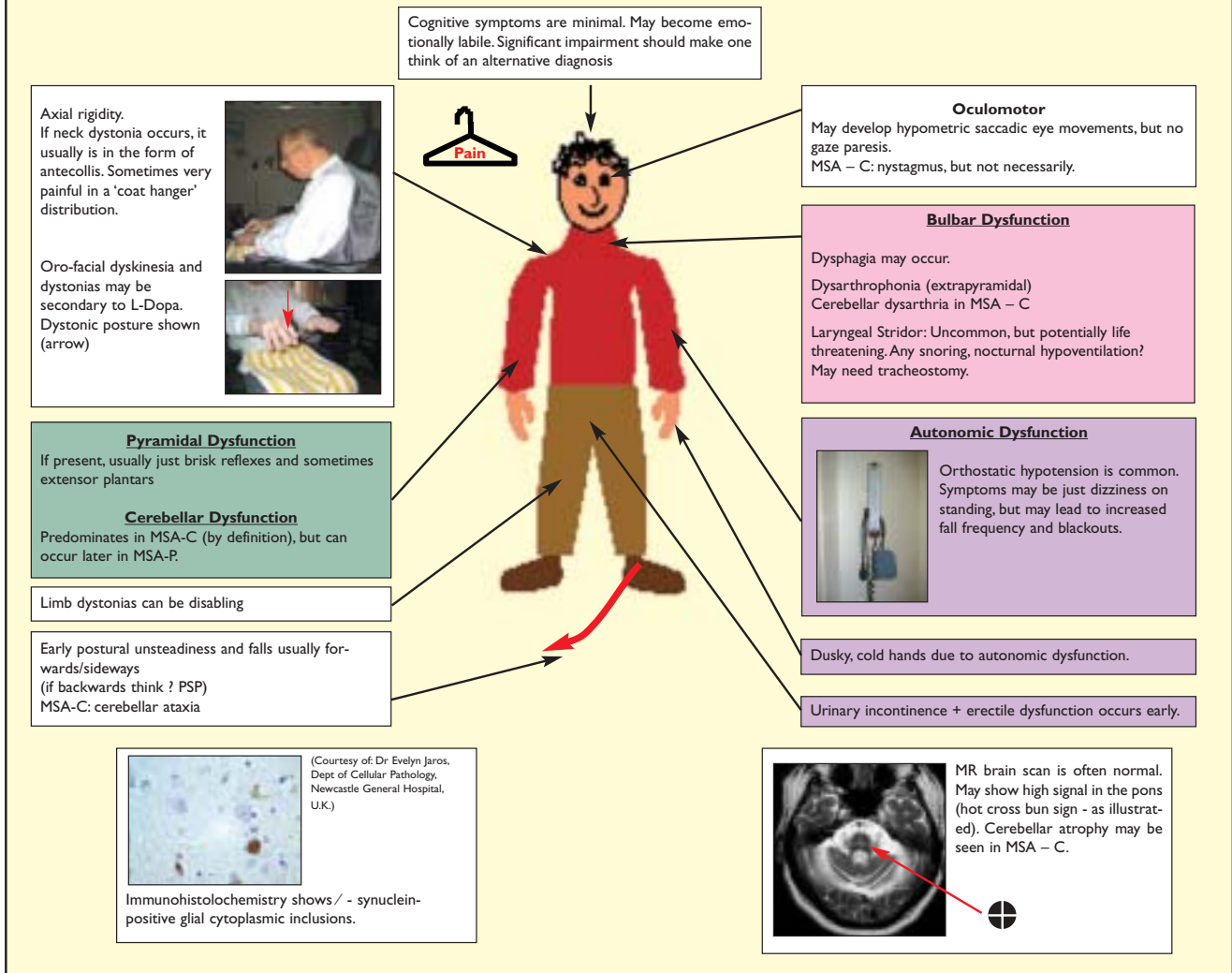
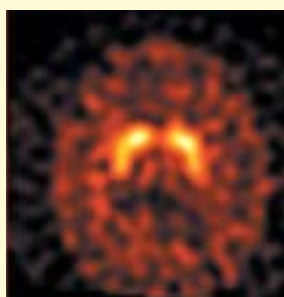
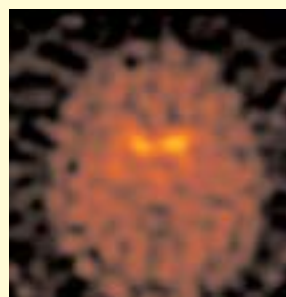


Figure 6: [I-123]FP-CIT SPECT (DaTSCAN™)



Normal



Parkinson's Disease

Figure 5: Dementia with Lewy Bodies (DLB)

Cognitive dysfunction

Early cortical cognitive dysfunction, especially:

- Executive
- Visuospatial (e.g. clock drawing)
- Memory impairment a later feature

Fluctuating **Confusion** (can vary from lucid to confused over a short time period)

Hallucinations (usually visual, but may be auditory, olfactory)

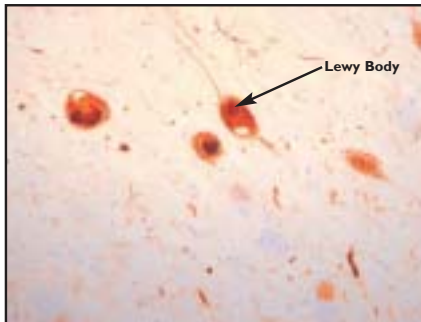


Spontaneous Parkinsonism

Occurs around or after onset of cognitive dysfunction

Other features (occur later in disease course):

- Antecollis
- Myoclonus
- Dysphagia
- Supranuclear Gaze Paresis (often can only differentiate between PSP and DLB at this stage via meticulous history from close carer of early cortical cognitive dysfunction).



Lewy Bodies

Immunohistochemistry shows α -synuclein-positive intra-neuronal inclusions, **Lewy bodies**, in the substantia nigra and cortex (as in IPD).

Pathologically, the frequency-density of cortical Lewy bodies defines the diagnosis, although degree of dementia does not correlate well with this.

(Immuno image courtesy of:
Dr Evelyn Jaros, Dept of Cellular Pathology,
Newcastle General Hospital, U.K.)

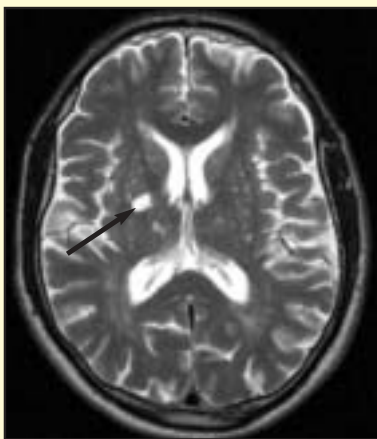


Figure 1: Vascular Parkinsonism

Multiple lacunar infarcts affecting the basal ganglia (arrow highlights largest one)
Sometimes may be coexistent with other AR syndromes making diagnosis difficult
Typically lower body Parkinsonism predominates with minimal tremor and less dopa responsive than IPD

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