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 one’s 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 not alter one’s 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 an 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-arigid 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 from symptom onset, although can be as little as 2 years.

Although 23% of IPD patients may never develop a tremor, 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. However, it 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%. 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 drowsy blue banity 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 response. Furthermore, patients with PSP or MSA may also respond to L-dopa, 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 acumen.

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 banity, nocturnal stridor, sighing, low amplitude myoclonic jerks (sometimes just affecting outstretched fingers when flicked by the examiner, termed polyminyoclonus) or significantly reduced blink rate. However, this does not negate the usefulness of criteria; the key features contained within them are important to know (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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Figure 2: Progressive Supranuclear Palsy (PSP)

Cognitive features: Frontal lobe symptoms and bradyphrenia. Memory only mildly affected (subcortical dysfunction).

Astonished facial expression

Torticollis and retrocollis

Vague eye symptoms: Blink rate very low, causing keratitis with photophobia, gritty sore eyes. Figure shows stippled fluorescein uptake in cornea, indicative of corneal desiccation

Urinary incontinence uncommon and late. (early autonomic dysfunction is rare and would point away from a diagnosis of PSP)

Vertical supranuclear gaze paresis

Very slow and hypometric saccades (difficulty tracking a line of text, vague eye symptoms, numerous visits to optician)

Dysphagia, often need enteral feeding. Commonest mode of death is aspiration pneumonia. Dysarthrophonia (growing in nature), with pallilalia. Speech becomes unintelligible

Early postural unsteadiness and falls (usually backwards)

Figure 3: Cortico Basal Degeneration (CBD)

Very asymmetric A-R syndrome with:
- Alien Limb (“my arm has a mind of it’s own”): arm elevates, hand grabs things and may interfere with activities of other hand
- Limb dystonia
- Myoclonus
- Dyspraxia
- Cortical Sensory loss

Occasionally, there may be features of PSP.

Both conditions share a similar pathology with tau deposition (4-repeat tau) and may be different ends of the spectrum of one disease process
### Table 1: Differential Diagnosis of Parkinsonism According to Identifiable Causes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology</th>
<th>Characteristic Clinical Features</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain Insult:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Vascular Parkinsonism</td>
<td>Infarcts in the nigro-striatal pathways</td>
<td>Acute onset, stepwise progression</td>
<td>Brain imaging (see fig 1)</td>
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<tr>
<td></td>
<td></td>
<td>Vascular risk factors</td>
<td>(Can be difficult though there is a high incidence of vascular disease in</td>
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<td></td>
<td></td>
<td>Lower body Parkinsonism</td>
<td>patients with IPD)</td>
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<td></td>
<td></td>
<td>Low incidence of tremor</td>
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<td></td>
<td></td>
<td>Poor L-Dopa response</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Can mimic any A-R syndrome</td>
<td></td>
</tr>
<tr>
<td>Cerebral Tumour</td>
<td>Basal ganglia, midbrain infiltration/compression</td>
<td>Can mimic any A-R syndrome</td>
<td>Brain imaging</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>unknown</td>
<td>Gait dyspraxia, dementia, urinary incontinence</td>
<td>Brain imaging</td>
</tr>
<tr>
<td>Pugilistic Parkinsonism</td>
<td>Repeated head trauma, possibly causing midbrain</td>
<td>Like IPD</td>
<td>Brain imaging shows evidence of previous midbrain haemorrhage.</td>
</tr>
<tr>
<td></td>
<td>contusions/haemorrhage</td>
<td></td>
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<tr>
<td><strong>Genetic Causes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Hepatic copper transport protein deficiency; inability</td>
<td>Young onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to excrete copper in bile, leading to copper deposition</td>
<td>Kaiser-Fleisher rings</td>
<td>Serum copper</td>
</tr>
<tr>
<td></td>
<td>in basal ganglia</td>
<td>Psychiatric features</td>
<td>24’ urine copper excretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tongue tremor</td>
<td>Serum Caeruloplasmin</td>
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<td>Liver biopsy</td>
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<tr>
<td>Parkin</td>
<td>Parkin mutation</td>
<td>Young onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autosomal recessive</td>
<td>Parkinson’s disease (44% of &lt;30 yr olds(12))</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Synuclein</td>
<td>– synuclein mutation</td>
<td>Very rare</td>
<td>Genetic testing</td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant</td>
<td></td>
<td></td>
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<tr>
<td>Westphal variant of</td>
<td>CAG repeat expansion in Huntington gene (function</td>
<td>Young onset, Family History</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Huntington’s disease.</td>
<td>unknown (autosomal dominant)</td>
<td>Late onset: may have myoclonus, dystonia, autonomic</td>
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<tr>
<td></td>
<td></td>
<td>dysfunction¹³</td>
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</tr>
<tr>
<td>Spinocerebellar ataxias,</td>
<td>SCA gene mutations</td>
<td>Parkinsonism and Cerebellar ataxia (may look like MSA-C)</td>
<td>Genetic Testing</td>
</tr>
<tr>
<td>type 2, 3 and 6</td>
<td></td>
<td>Family History</td>
<td></td>
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<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
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<tr>
<td>Whipples disease</td>
<td>The bacterium <em>Tropheryma whippleii</em></td>
<td>Can present like PSP</td>
<td>PAS +ve macrophages on duodenal biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other neurological features: neuropathy, myopathy,</td>
<td>PCR of CSF</td>
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<td></td>
<td></td>
<td>Orofacial myorhythmia</td>
<td></td>
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<td></td>
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<td>Gastrointestinal disturbance</td>
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<tr>
<td>Post encephalitic</td>
<td>Unknown virus</td>
<td>Previous history of encephalitis Other movement</td>
<td>Essentially clinical</td>
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<td></td>
<td></td>
<td>disorders</td>
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<tr>
<td>CJD¹⁴</td>
<td>Prion disease</td>
<td>Psychiatric features, myoclonus, supranuclear gaze</td>
<td>Pulvinar high signal on MR scan with nvCJD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>paresis</td>
<td>14-3-3 protein in CSF</td>
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<tr>
<td><strong>Toxin</strong></td>
<td></td>
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<tr>
<td>Neuroleptics and other</td>
<td>Dopamine receptor blockade</td>
<td>Like IPD</td>
<td>Withdraw drug if possible May take up to 15 months for Parkinsonism to</td>
</tr>
<tr>
<td>drugs</td>
<td></td>
<td></td>
<td>resolve DaTscan to differentiate from IPD</td>
</tr>
<tr>
<td>Manganese Carbon Disulphide</td>
<td>Direct neurotoxic effects</td>
<td>Headaches, psychiatric disorders CS: also neuropathy</td>
<td>History of exposure</td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>Ischaemic damage to basal ganglia</td>
<td>Like IPD, very severe, symmetrical</td>
<td>From clinical history ?gas fire at home. Imaging shows basal ganglia</td>
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<tr>
<td></td>
<td></td>
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<td>infarcts.</td>
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</tbody>
</table>
**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**

**Cognitive symptoms** are minimal. May become emotionally labile. Significant impairment should make one think of an alternative diagnosis.

**Pyramidal Dysfunction**

If present, usually just brisk reflexes and sometimes extensor plantar.

**Cerebellar Dysfunction**

Predominates in MSA-C (by definition), but can occur later in MSA-P.

Limb dystonias can be disabling.

Early postural unsteadiness and falls usually forwards/sideways (if backwards think ? PSP)

**MSA-C: cerebellar ataxia**

Axial rigidity.

If neck dystonia occurs, it usually is in the form of antecolls. Sometimes very painful in a ‘coat hanger’ distribution.

Oro-facial dyskinesia and dystonias may be secondary to L-Dopa.

**Pyramidal Dysfunction**

Dystonic posture shown (arrow).

**Oculomotor**

May develop hypometric saccadic eye movements, but no gaze paresis.

**MSA – C: nystagmus, but not necessarily.**

**Bulbar Dysfunction**

Dysphagia may occur.

Dysarthrophonia (extrapyramidal)

Cerebellar dysarthria in MSA – C


**Autonomic Dysfunction**

Orthostatic hypotension is common.

Symptoms may be just dizziness on standing, but may lead to increased fall frequency and blackouts.

Dusky, cold hands due to autonomic dysfunction.

Urinary incontinence + erectile dysfunction occurs early.

**MR brain scan is often normal.**

May show high signal in the pons (hot cross bun sign - as illustrated). Cerebellar atrophy may be seen in MSA – C.

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

Normal

Parkinson’s Disease

(Courtesy of Dr Evelyn Jaros, Dept of Cellular Pathology, Newcastle General Hospital, UK.)

Immunohistolochemistry shows α-synuclein-positive glial cytoplasmic inclusions.
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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 -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

With thanks to Dr David Burn for his assistance in preparing this Management Topic.