PITFALLS IN THE DIAGNOSIS OF PARKINSON'S DISEASE

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The purpose of this handout and accompanying lecture is to improve your ability to diagnose Parkinson's disease. This will be accomplished in two ways: first, by reviewing the new MDS diagnostic criteria for PD, and second, by highlighting three common diagnostic pitfalls: 1) failure to recognize drug-induced parkinsonism; 2) confusing PD with essential tremor, and 3) distinguishing PD from a parkinsonian syndrome (PSP, MSA, etc.).

Parkinson's disease is generally assumed to be a straightforward, "waiting room" diagnosis. In support of this, consider that in his description of The Shaking Palsy, exactly 200 years ago, James Parkinson reported the details of 6 people with *paralysis agitans*, only 3 of whom he had seen as patients; the others were encountered in the streets of London, as Parkinson recognized their distinctive physical features. In contrast to the generally held belief that diagnosing PD is easy, autopsy studies have shown that up to 20% of patients diagnosed as having PD during life prove to have an alternative diagnosis—usually a parkinsonian syndrome; the misdiagnosis rate is even higher (over 1/3) if only the initial diagnosis is considered. Making an early, accurate diagnosis of PD is not just a challenge for the general neurologist; clinical trials conducted by movement disorders specialists, using dopamine transporter imaging as the "gold standard" (yes, it is not perfect) have demonstrated a misdiagnosis rate ranging from a low of 3.6% to as high as almost 20%. Yet, when a patient is followed long-term by a movement disorder specialist, the positive predictive value of the last clinical diagnosis prior to death, compared to the autopsy, is nearly 100%. This demonstrates that diagnostic accuracy hinges largely on having familiarity with the characteristic features of PD, recognizing symptoms and signs at onset and especially during follow-up that cast doubt on the diagnosis ("red flags"), and continuously reevaluating the diagnosis over time.

What are the reasons that a disease as common as PD is so commonly misdiagnosed?

1. Since PD is largely an outpatient condition, residents get relatively exposure to it during training, and especially early PD. In fact, many residents graduate without ever having had the opportunity to make the diagnosis of PD.

2. The earliest symptoms and signs of PD are subtle and unless one suspects it, they are often overlooked—decreased arm swing on one side, a little slowing of finger or toe tapping, a slightly decreased blink rate, a soft voice. It can take time for the disease to "blossom" to the point where the diagnosis is considered. But, like most of medicine, one's ability to make a diagnosis requires a "prepared mind" and this means familiarity with the early symptoms and signs of PD.

3. Inadequate history and examination. This leads to two types of errors. First, false positives: the patient is diagnosed with PD when in fact they have an alternative (related) diagnosis. Examples include failure to take a careful drug history and therefore missing the diagnosis of drug-induced parkinsonism; or, lack of familiarity with or looking for "red flags" which cast doubt on the diagnosis of PD and point towards a parkinsonian syndrome such as MSA-P, PSP, CBS or DLB. For instance, not screening for dysautonomia or paying enough attention to eye movements. Second are false negatives: the patient has PD but because it may be a bit atypical, this diagnosis is not considered. This includes young-onset PD, a sensory presentation, such as shoulder pain, atremulous PD, or PD beginning in the lower extremity (foot tremor), among others. In this circumstance, patients are often diagnosed as having a stroke, spinal or peripheral problem, or a rheumatologic condition and end up undergoing unnecessary testing before it becomes clear that the problem is PD.

4. Lack of a specific biomarker for PD (note, DaTSCAN™ cannot distinguish PD from a parkinsonian syndrome). We have become very reliant on imaging and other objective tests to make neurologic diagnoses and as such, there seems to be less confidence in making a *clinical* diagnosis, which is the case with PD.

5. Failure to reconsider the diagnosis of PD at each visit. Parkinsonian syndromes may look like PD early on but with time, their distinctive features become more obvious, and the natural history deviates from that expected with PD.

MDS Diagnostic Criteria for PD

It is essential to be familiar with the new Movement Disorders Society clinical diagnostic criteria for PD published in 2015. Although yet to be validated (the gold standard to be used is the clinical diagnosis by experts), these represent an important update since the UK Brain Bank Criteria proposed in 1988. A complete discussion of the criteria is beyond the limits of this course. Table 1 of the criteria (see Postuma RB, et al) is a very useful guide that takes the examiner step-by-step through the process of diagnosis. There are two levels of diagnostic certainty: *clinically established* and *probable* PD distinguished by the degree to which certain features are present or absent (e.g. number of "red flags"). There are four basic steps in the diagnosis. First is to establish that the patient in fact has parkinsonism defined as bradykinesia accompanied *either* rigidity *or* resting tremor. The second step is the presence of supportive criteria including a "clear and dramatic beneficial response to dopaminergic therapy." Other supportive features include the eventual appearance of levodopa-induced dyskinesias, the presence of a rest tremor, and positive results from at least one ancillary test such as smell or cardiac MIBG scintigraphy (note, only two supportive criteria are needed for clinically established PD so additional testing is not necessary). Third is the lack of "absolute exclusionary criteria," that is, any feature which is not expected with PD such as cerebellar signs, supranuclear ophthalmoplegia, cortical sensory loss, etc. Additional exclusionary criteria include exposure to a dopamine blocking agent in a time course that could explain the findings; absent response to high-dose levodopa, and normal functional imaging of the presynaptic dopamine system. Regarding imaging, *it is important to note that the criteria do not necessitate the performance of imaging* but if such imaging is done, and if normal, then that "rules out" PD, but, there are some caveats about DA transporter imaging discussed below. Note that the presence of any of the "absolute exclusion criteria … rules out PD" according the MDS criteria.

The fourth and final criterion concerns "red flags." As discussed below, in the section on parkinsonian syndromes, these are clinical features that cast doubt on the diagnosis of PD and usually point toward a parkinsonian syndrome (they overlap with the third criterion above). They include rapid progression (faster than PD), early falls, early autonomic failure, early bulbar dysfunction, symmetrical parkinsonism, and others. Most red flags indicate the *presence* of an atypical sign, but the MDS criteria also specify the *absence of a non-motor sign* of *PD* as a red flag, as well. For instance, not observing hyposmia, a REM behavioral disorder, autonomic dysfunction including constipation, urinary urgency and ED (the line between autonomic dysfunction and failure viz. MSA, can be blurry) or neuropsychiatric features (depression, anxiety and late hallucinations) are red flags.

One area of controversy with the new criteria concerns the timing of dementia. Traditionally, early dementia was considered a red flag pointing away from PD suggesting instead DLB, FTD with parkinsonism, or AD with parkinsonism, but in the new criteria, dementia is no longer an exclusionary feature "… regardless of when it occurs in relation to parkinsonism onset." To a large degree this reflects two aspects of PD; first, the somewhat arbitrariness of setting a one year limit between parkinsonism and dementia for DLB, and second, recent recognition that cognitive impairment (MCI more than frank dementia) can be seen early in the course of PD, in some people. Personally, I remain hesitant to diagnose PD if there is dementia early in the course— this is more likely DLB, a dual diagnosis of PD and either AD or vascular dementia, or vascular parkinsonism/dementia. Having voiced this reservation, the way the criteria are constructed, most causes of parkinsonism and dementia, which are not due to PD, will likely fail to reach other criteria necessary for the diagnosis of PD so this may prove to be a moot point. Furthermore, reflecting the clinical wisdom of the authors who designed the criteria, they left the PD diagnostic door a bit ajar by including under absolute exclusion criteria: "Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD." As such, there is a place for clinical judgment vs strict adherence to clinical criteria, particularly since there is no biomarker for PD.

Imaging of the Presynaptic Dopamine Transporter

A personal comment on imaging of the pre-synaptic dopamine transporter. In the US, DaTSCAN™ is approved for differentiating PD from ET but this is rarely a clinical conundrum and as discussed below, the two can almost always be distinguished on clinical grounds, with rare exceptions. In my practice, I see far too many DaTSCANs™ done needlessly—often for straightforward cases of PD or ET. According to the MDS diagnostic criteria for PD, a DaTScan is not required. There are some off-label situations where a DaTSCAN™ can be useful such as distinguishing PD from drug-induced parkinsonism, or distinguishing "parkinsonism" due to NPH or vascular disease from parkinsonism associated with nigrostriatal degeneration. A DaTSCAN™ can be considered if: 1) there is legitimate confusion over the diagnosis; 2) if the result will change management; and 3) if the information cannot be obtained in another more convenient and less expensive way such as the "test of time" or consultation with a movement disorders specialist. It is important to note that a DaTSCAN™ cannot distinguish PD from other causes of parkinsonian associated with nigrostriatal degeneration including MSA, PSP and CBS. In most cases when the cause of parkinsonism is not clear, the main question is whether it is PD or a parkinsonian syndrome, and the DaTSCAN™ will not give the answer.

Three Common Pitfalls in the Diagnosis of Parkinson's Disease

Pitfall #1: drug-induced parkinsonism (DIP)

- The two key steps are having an index of suspicion and taking a good drug history.
- DIP may persist for one year after the offending drug is discontinued so the patient may not be on the medication at the time of the visit. It is important to ask about use of "nerve pills… sleeping pills… nausea pills" within the last year.
- It may require sleuthing to get a drug history
    - Have the patient bring in all their medications ("clean out the medicine cabinet")
    - Get notes from the primary care doctor or psychiatrist
    - Get pharmacy records
- Although DIP is usually symmetrical and atremulous, it can look just like PD with classic rest tremor and asymmetry
- The most common cause of DIP today is the "atypical" antipsychotics. It is important to appreciate that "atypical" antipsychotics can cause all of the "typical" extrapyramidal side effects. Metoclopramide and other anti-DA antiemetics can cause parkinsonism (and tardive syndromes). Less well appreciated is that lithium and valproic acid can also cause parkinsonism.
- Be careful not to withdraw the offending medication abruptly (and only after consultation with the patient's psychiatrist) as this can cause withdrawal emergent tardive dyskinesia.
- Drug-induced parkinsonism can take up to one year to reverse. If it persists after that, it is likely that the patient has another cause of parkinsonism, such as PD, which might have been exacerbated by medication.
- While an off-label indication, a DaTSCAN™ can be used to differentiate DIP from parkinsonism associated with nigrostriatal degeneration. Yet, before pursuing this, it is important to ask whether the result will change management— if the drug will be stopped no matter the result, then the best "test" for DIP vs another cause of parkinsonism might be the test of time.

Pitfall #2: Is it PD or ET?

- The differential diagnosis of tremor in an adult usually boils down to PD vs ET.
- The table below emphasizes the distinguishing features from the history and examination.
- Historically, ET is often present for years or even decades before the patient seeks medical attention whereas patients with PD (who have tremor) typically seek medical attention within 6-12 months. So, a long duration of tremor suggests ET.
- The family history is more likely to be positive in ET.
- ET often improves temporarily with a small amount of alcohol which usually does not improve a PD tremor
- One particularly helpful clue is that PD begins unilaterally or at least very asymmetrically whereas ET is almost always bilateral at onset (the patient may not appreciate it in the non-dominant hand but this is seen on examination). So, a unilateral tremor (of the hand, forearm, or foot) is likely PD.

- Tremor of the head and voice (when accompanied by tremor of the UEs) is usually ET whereas tremor of the jaw, lips or tongue is seen in PD. The PD tremor is often present while the patient walks, unlike ET.
- PD is a rest tremor whereas ET is maximally activated with maintenance of posture and movement.
- Just to confuse things, the rest tremor of PD may "reemerge" after maintaining posture for 5-10 seconds. A PD reemergent postural tremor is unilateral (assuming the rest tremor is as well) and has the same frequency and morphology as the rest tremor. It usually suppresses with movement.
- It is not too uncommon to have a slightly faster postural or kinetic tremor with otherwise typical PD. There is some controversy about this—whether this should be called concurrent ET or all part of PD. I favor the latter.
- ET can sometime be seen at rest under several circumstances. First, if there is a mild proximal LE tremor—this can be subtle but if present, the hands only shake because they are resting on tremulous legs; second, the patient may not be completely at rest and if so, encouraging them to relax their limbs should make it go away; and third, some patients with longstanding ET will develop a bona fide resting tremor, akin to a PD tremor.
- A handwriting sample is usually enough to distinguish PD from ET. The former is atremulous and small (assuming the dominant hand is effected) whereas ET is of normal size but tremulous, as is an Archimedes spiral.

Feature	PD	ET
Usual duration of symptoms prior to medical contact	6-12 months	Usually several years or more
Family history	Generally negative (5-15% with an affected first degree relative)	Often positive (>60%), autosomal dominant
Response to small amount of alcohol	Little or none	Often improves
Position of maximal activation	Rest	Maintenance of posture or with movement
Frequency	3-6 Hz	6-12 Hz
Morphology	Pill-rolling	Flexion-extension
Onset	Unilateral	Bilateral
Body part(s) affected	Upper limb, lower limb, chin, lips or tongue	Upper limb, head, voice,
Handwriting	Micrographic, atremulous	Normal size, tremulous
Associated signs (bradykinesia, hypomimia, etc.)	Present	Absent
Is the tremor present when walking?	Yes	NO

Pitfall #3: PD vs a Parkinsonian Syndrome

- The most common mimicker of PD is a parkinsonian syndrome (PS).
- It is important to be familiar with the clinical features of the most common PS: MSA, PSP and CBS (see references for diagnostic criteria) and the "red flags" that cast doubt on the diagnosis of PD

- **MSA: Autonomic failure (OH or urinary incontinence [and ED] with either parkinsonism, which does not improve with levodopa*, or a cerebellar syndrome**
    - The most common pitfall referable to MSA is inadequate attention to autonomic symptoms and signs. Checking for OH is key—it is remarkable how asymptomatic patients can be despite significant OH; ask about bladder and sexual function.
    - *Early on, there can be improvement with levodopa, usually not as dramatic as with PD, and the benefit tends to wane.
    - An important clue about MSA is a more rapid decline than seen with PD
    - Other features: cold dusky hands; inspiratory stridor and sighs; low amplitude, jerky postural tremor; "squeaky" voice; limb contractures; anterocollis.

    - It may affect younger patients (late 40s or early 50s) and when it does, the diagnosis is often not considered.
- **Progressive supranuclear palsy**
    - Typical presentation is early falls, axial > appendicular rigidity and bradykinesia, and supranuclear vertical ophthalmoplegia (Richardson's syndrome)
    - Other presentations: may look like CBD with limb apraxia; can present as gait freezing—"pure akinesia;" a picture suggesting FTD, or like PD early on.
    - The key diagnostic finding is supranuclear vertical ophthalmoplegia but before there is actual limitation of vertical gaze (including downward, not just up), there is slowing of vertical saccades.
    - To look for slowing of vertical saccades, compare saccades with the patient looking between horizontal targets vs vertical targets—the latter will appear more difficult and slower; this can also be brought out with OKN, noting the absence of fast phases when the tape is moved vertically vs. horizontally.
    - Pursuit eye movements are disproportionately preserved in PSP so having the patient follow a target will miss the key finding of slow saccades
    - Other features of PSP: frontal lobe findings (impulsivity, impaired verbal fluency, concreate proverb interpretation); robotic voice; eyelid opening apraxia; retrocollis; applause sign (when asked to clap just three times, patients continue clapping).
- Corticobasal syndrome
    - Because there is not a good correlation between the clinical diagnosis of corticobasal denegation and pathological confirmation, during life it is referred to as corticobasal *syndrome* recognizing that several pathologies can produce such a picture including PSP, FTD and AD
    - Classic picture combines cortical and basal ganglia signs: a unilateral, useless, rigid, dystonic, jerky arm with parietal lobe sensory loss
    - Varied presentation with motor signs (myoclonus, dystonia, rigidity, apraxia—often starting unilaterally) and cortical: aphasia, dementia, parietal lobe sensory loss (agraphesthesia, asterognosis—check for them)

What are the red flags casting doubt on the diagnosis of PD?

- Lack of benefit from levodopa
    - Adequate trial is ~1000mg per day, given during active hours
    - Note that large amplitude PD tremor may not respond well to levodopa, but PD is not ruled out in this circumstance
- Early falls
    - Falls are common in PD but usually in the middle and latter stages
    - Early falls suggest PSP
- Rapid progression
    - "Wheelchair sign"
    - If a patient with "PD" comes to the office in a wheelchair within 3-5 years of disease onset, consider a PS
- Early bulbar dysfunction
    - Impaired speech and swallowing are common in PD but usually not a significant problem early on unlike PS in which bulbar dysfunction is common early—significant dysarthria and/or dysphagia
    - Inspiratory stridor and sighs suggest MSA; inquire about sleep apnea
- Early autonomic failure
    - Like falls and bulbar dysfunction, autonomic dysfunction is common in PD but usually not particularly problematic within the first five years
    - When there is problematic dysautonomia early, especially OH and urinary incontinence, consider MSA
- Early dementia
    - As mentioned above, in the new MDS diagnostic criteria, the timing of dementia, including at presentation, does not rule out PD
    - Nevertheless, if there is dementia preceding or very early into the course, while it may be PD, this should be considered a red flag suggesting DLB, AD, a multi-infarct state, NHP, etc.
- Early psychosis
    - This is a late complication of PD, usually in the presence of cognitive impairment
    - Early psychosis should raise suspicion of DLB

- Supranuclear vertical ophthalmoplegia
    - See above re: PSP
    - Before actual ophthalmoplegia, there is slowing of saccades and when searched for, this allows for an earlier diagnosis of PSP
- Signs outside of the nigrostriatal pathway
    - Aphasia, apraxia, pyramidal signs, cerebellar signs, cortical sensory loss
- Movement disorders usually not seen in PD
    - Significant dystonia (especially fixed dystonia)
    - Blepharospasm or eyelid opening apraxia
    - Retrocollis or anterocollis
    - Pisa syndrome (severe lateral leaning of posture)
    - Myoclonus
- Symmetrical onset of parkinsonism
- Lower half parkinsonism
    - This refers to parkinsonism from the waist down but to a much lesser extent from the waist up
    - Often seen in older patients
    - Often have broad base rather than the narrow base of PD
    - Consider NPH or vascular parkinsonism

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