Differential Diagnosis of Parkinson's Disease: A New Blood Test?

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Parkinson's disease (PD) is a common disorder that should be, and usually is, easy to diagnose. The clinical features first described by James Parkinson in 1817 continue to apply today. The most widely accepted modern version is from the UK Parkinson's Disease Society Brain Bank¹ whose criteria for a diagnosis of Parkinson's disease are bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:

- muscular rigidity on passive range of motion,
- 4-6 Hz resting tremor,
- postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive function.

A variety of exclusion criteria (e.g., history of repeated strokes, repeated head trauma, encephalitis, neuroleptic use and abnormal neuroimaging) as well as supportive criteria (e.g., unilateral onset and levodopa responsiveness) can help to weaken or strengthen the presumptive diagnosis. Nevertheless, clinicopathologic studies have demonstrated that even in the best of hands the correct diagnosis is missed in approximately 20% of cases.^{2,3} Disorders like progressive supranuclear palsy and the multiple systems atrophy syndromes (i.e., striatonigral degeneration, olivopontocerebellar atrophy, Shy-Drager syndrome, corticobasal degeneration) make up the remaining 20% that are often misdiagnosed.

The importance of making the correct diagnosis is at least three-fold:

1. *Proper diagnosis*: Making the correct diagnosis allows for proper prognostication and management. The atypical parkinsonian disorders are typically earlier in onset and have a more fulminant course than routine idiopathic PD. Problems facing individuals afflicted with one of these disorders are more likely to include early dysautonomia, bulbar dysfunction, respiratory compromise, spasticity, ataxia and

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apraxia. Knowing the correct diagnosis allows the treating physician to deal proactively with issues such as quality of life, feeding and other end-of-life questions that will almost certainly come sooner than later compared to idiopathic PD.

2. *Medical treatment:* The atypical parkinsonian disorders are generally unresponsive to pharmacotherapy. Having a tool to help confirm or reject the diagnosis of PD would clearly help guide rational medical management. If such a tool would be suggestive of idiopathic PD, the clinician might be inclined to be more aggressive in treatment, as typical PD can be expected to respond to at least one of the many pharmacologic options available. In contrast, a decision to limit trials of medication might be made with the atypical syndromes—thus sparing the patient from unwanted side-effects, ineffective results and unnecessary cost.
3. *Surgical treatment:* Deep Brain Stimulation is one of the most important modalities for treating PD since the advent of levodopa in the late 1960's. However, results from several studies make it clear that benefit from this invasive and potentially risky procedure is dependent upon 2 factors: proper diagnosis of PD and precise localization of the stimulating electrode. Patients with any of the atypical parkinsonian syndromes do not benefit from deep brain stimulation, and it is crucial to have an accurate diagnosis prior to surgery.

Currently, we have no reliable adjunctive tools to help us accurately distinguish the atypical parkinsonian disorders from idiopathic PD. Standard magnetic resonance imaging or computed tomography studies have limited usefulness. More expensive and often research-based technologies like positron emission tomography, single photon emission computed tomography scans or functional magnetic resonance imaging studies do not yet have a practical place in making these diagnoses; blood work and cerebral spinal fluid studies are currently of no value. A good history and physical examination, along with assessment of levodopa responsiveness, remain our strongest tools.

Nevertheless, in this issue of *Clinical Medicine & Research*, Pellecchia and colleagues⁴ review data which provocatively suggest that indeed there may be a relatively simple adjunctive test to assist in differential diagnosis of parkinsonian disorders: measuring serum growth hormone (GH) levels in response to challenge with clonidine or arginine. These agents both act physiologically as GH secretagogues, and while idiopathic PD patients demonstrate essentially normal responses over the course of 1 hour, the atypical syndromes do not show the expected rise in GH.

The literature is still small and somewhat controversial, but the review by Pellecchia et al⁴ helps shed light on an area of marked importance in neurology and will hopefully stimulate future studies. As in most things medical: more work is required.

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