

Primary Autonomic Failure: Three Clinical Presentations of One Disease?

Three neurodegenerative diseases of unknown cause involve primary autonomic failure. These diseases are pure autonomic failure, in which autonomic impairment (that is, orthostatic hypotension and bladder and sexual dysfunction) occurs alone; Parkinson disease, in which autonomic failure is combined with an extrapyramidal movement disorder; and multiple-system atrophy (also called Shy–Drager syndrome), in which autonomic failure is combined with an extrapyramidal or cerebellar movement disorder or both (1).

During the early stages of multiple-system atrophy, autonomic deficits may be the sole clinical manifestation; therefore, the disease may resemble pure autonomic failure. However, after a variable period that can be as long as several years, extrapyramidal or cerebellar deficits or both invariably develop. In Parkinson disease, extrapyramidal motor problems are the presenting feature; later in the disease process, patients may develop severe autonomic failure, making it difficult to distinguish between Parkinson disease and multiple-system atrophy. To further complicate the distinction, some patients with multiple-system atrophy display motor deficits similar to those seen in Parkinson disease before autonomic failure is apparent.

In clinical practice, all of these possibilities lead to two main diagnostic problems. First, it cannot be determined whether a patient who is thought to have pure autonomic failure and whose only finding is autonomic failure will develop more widespread nonautonomic neuronal damage and be found to have multiple-system atrophy. Second, it may be difficult to determine whether a patient with autonomic failure and a parkinsonian movement disorder has Parkinson disease or multiple-system atrophy.

In addition to clinical criteria, several tests have been used to distinguish among Parkinson disease, pure autonomic failure, and multiple-system atrophy. For example, vasopressin release in response to hypotension and growth hormone secretion in response to clonidine are blunted in multiple-system atrophy but preserved in pure autonomic failure and Parkinson disease. This is because brain stem–hypothalamic–pituitary pathways are affected only by multiple-system atrophy (2, 3). Plasma norepinephrine concentration while supine is low in patients with pure autonomic failure but normal in patients with multiple-

system atrophy because postganglionic neurons are normal (4). Sphincter electromyography shows denervation in multiple-system atrophy because the Onuf nucleus in segments S2 to S4 of the spinal cord is affected; however, it is normal in Parkinson disease (5). In addition, magnetic resonance imaging of the brain shows abnormalities in the putamen only in multiple-system atrophy (6).

However, most if not all of these tests are frequently ambiguous, and accurate methods to distinguish Parkinson disease from other diseases with extrapyramidal involvement, particularly multiple-system atrophy, are necessary. Differential diagnosis of extrapyramidal and autonomic disorders is important because of prognostic purposes and because accurate diagnoses are required when testing new surgical and pharmacologic therapies. In a thorough and elegant study in this issue, Goldstein and colleagues (7) show that sympathetic cardiac innervation is selectively affected in Parkinson disease and pure autonomic failure but not in multiple-system atrophy. This may be a useful diagnostic test that can distinguish between Parkinson disease and multiple-system atrophy. Moreover, in a patient with apparent pure autonomic failure, normal sympathetic cardiac innervation should indicate probable development of multiple-system atrophy.

To visualize the sympathetic innervation of the heart, the investigators used thoracic positron emission tomographic scanning after intravenous infusion of 6-¹⁸F]fluorodopamine, a catecholamine taken up by sympathetic postganglionic neurons and handled in a manner similar to the way in which norepinephrine is handled. In addition, the investigators performed cardiac catheterization to determine cardiac norepinephrine spillover, extraction of [³H]norepinephrine, and venous–arterial differences in levels of plasma dihydroxyphenylglycol (DHPG, a marker of neuronal norepinephrine turnover) and L-dopa (a marker of norepinephrine synthesis in sympathetic nerves). Of 29 patients with Parkinson disease, 9 had chronic orthostatic hypotension (only 4 were taking L-dopa). Of the remaining 20 patients with Parkinson disease (those without orthostatic hypotension), 15 were taking L-dopa. As expected, most patients with multiple-system atrophy had orthostatic hypotension, 5 of whom were taking L-dopa.

Goldstein and colleagues found that all patients with Parkinson disease and orthostatic hypotension as well as most patients with Parkinson disease and no orthostatic hypotension had loss of functional cardiac sympathetic nerve terminals. This was shown by decreased myocardial concentration of 6-[¹⁸F]fluorodopamine–derived radioactivity as well as decreased cardiac extraction of [³H]norepinephrine, norepinephrine spillover, and cardiac venous–arterial differences in plasma levels of DHPG and L-dopa. Myocardial concentrations of 6-[¹⁸F]fluorodopamine–derived radioactivity were as low in patients with Parkinson disease as in patients with pure autonomic failure. In marked contrast, all patients with multiple-system atrophy had normal 6-[¹⁸F]fluorodopamine–derived radioactivity that was similar to that in normal controls.

Similar results were seen in several studies from different laboratories that used single photon-emission computed tomographic imaging with ¹²³I-metaiodobenzylguanidine (8–10), as well as in an earlier study by Goldstein and colleagues (11) that used 6-[¹⁸F]fluorodopamine positron emission tomography. However, these studies included a small number of patients. More important, questions remained about the possibility that chronic L-dopa treatment accounted for these findings in Parkinson disease. In their present study, Goldstein and colleagues show that the abnormal cardiac sympathetic innervation detected by positron emission tomography is not related to long-term L-dopa administration: The defect was also evident in patients with Parkinson disease who were not taking L-dopa. Moreover, patients with multiple-system atrophy who were taking L-dopa had normal cardiac sympathetic innervation.

Scanning of the heart with positron emission tomography distinguishes between Parkinson disease and multiple-system atrophy because sympathetic innervation is impaired in the former but not the latter. Goldstein and colleagues' finding of loss of functional cardiac sympathetic nerve terminals in Parkinson disease also confirms that the degenerative process of this disease extends well beyond central dopaminergic systems to involve peripheral catecholamine-containing neurons. The results further indicate that multiple-system atrophy exclusively affects neurons in the central nervous system. In multiple-system atrophy, sympathetic responses are abnormal because peripheral autonomic neurons, although intact, are not engaged by the central nervous system.

Despite all these clinical and pathologic differences,

are these three diseases different entities? The neuropathologic markers in multiple-system atrophy are glial and neuronal cytoplasmic inclusions in the central nervous system; peripheral sympathetic postganglionic neurons are spared (12). In contrast, in Parkinson disease and pure autonomic failure, a different type of cytoplasmic inclusion (Lewy bodies) is found in the central nervous system as well as in peripheral autonomic ganglia and postganglionic sympathetic neurons (13–15).

Recent findings suggest that the same neurodegenerative process underlies multiple-system atrophy, Parkinson disease, and pure autonomic failure because in all three, α -synuclein accumulates in the neuronal cytoplasmic inclusions. A gene encoding for α -synuclein, a neuronal protein of unknown function, is mutated in autosomal dominant Parkinson disease (16). Nonfamilial Parkinson disease does not have the mutation, but α -synuclein accumulates in Lewy bodies in these patients, suggesting a toxic role for aggregates of this protein (17). Of interest, it was recently reported that cytoplasmic inclusions in multiple-system atrophy also stain positive for α -synuclein (18), and other researchers have found that Lewy bodies in pure autonomic failure are strongly positive for α -synuclein (Kaufmann and coworkers. Unpublished data). Thus, abnormalities in the expression or structure of α -synuclein or associated proteins may cause degeneration of catecholamine-containing neurons. It is therefore possible to speculate that primary autonomic failure includes three clinical presentations of one disease. Elucidation of the role of α -synuclein in neuronal degeneration may test this hypothesis. Meanwhile, tests that contribute to accurate diagnoses of the different forms of autonomic failure will greatly facilitate evaluation of new therapies.

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