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Pure autonomic failure without alpha-synuclein pathology: an evolving understanding of a heterogeneous disease

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Victorian philosopher Herbert Spencer wrote “evolution is a progress from an indefinite, incoherent homogeneity toward a definite, coherent heterogeneity”. In this issue of *Clinical Autonomic Research*, Isonaka *et al.* describe a case of pure autonomic failure (PAF) that lacks α-synuclein deposition on autopsy, which may further define the heterogeneity in PAF [5].

Over the past century, the understanding and definition of PAF has evolved. Since the 1925 description of postural hypotension by Bradbury and Eggleston, multiple etiologies have been linked to idiopathic orthostatic hypotension [2, 10]. The current consensus criteria established in 1996 defines PAF as a disorder characterized by chronic neurogenic orthostatic hypotension due to sympathetic denervation without evidence of central neurodegeneration [6].

Pathologically, several reports have documented the presence of α-synuclein positive inclusions in PAF [4]. α-synuclein, in the form of Lewy bodies and Lewy neurites, has been confirmed in sympathetic ganglia and postganglionic sympathetic axons as well as in the central nervous system. Intraneural α-synuclein has even been reported on skin biopsy in PAF although consistent reproducibility has been difficult [3]. With these findings, PAF has been classified as a synucleinopathy. Recent reports have detailed the evolution of certain PAF patients and their phenotype into other synucleinopathies with widespread CNS involvement such as Parkinson disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB) [7, 8]. While these large studies have strengthened the categorization of PAF as a synucleinopathy, it is important to note that not all patients with PAF eventually develop central neurodegeneration.

The case report in this issue by Dr. Goldstein’s group challenges the notion that all cases of PAF are in the synucleinopathy spectrum by demonstrating a case that meets consensus criteria for PAF with no pathologic deposition of α-synuclein. Clinically, this patient was a middle-aged man who developed urogenital dysfunction shortly followed by symptomatic orthostatic hypotension. Notably, dream-enactment behavior was reported but neither symptoms nor sign of motor or cognitive impairment were present. The patient was thoroughly studied with repeat assessment in 3 years. One of the strengths in this case is the

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thorough and longitudinal catecholamine assessment; norepinephrine and 3,4-dihydroxyphenylglycol (DHPG) were low both peripherally and centrally with a decline at follow-up testing while plasma dopamine levels increased. There was also evidence of cardiac sympathetic denervation and reduced sympathetic dermal innervation of arrector pili muscles. Interestingly, postganglionic sympathetic sudomotor testing measured by quantitative sudomotor axon reflex testing (QSART) was normal throughout the disease course. The neuropathological findings are thought provoking. α-synuclein was lacking from the brain, brainstem, sympathetic ganglia and myocardial tissue despite loss of sympathetic ganglion tissue and sympathetic innervation of the heart. Skin biopsy was also negative for α-synuclein.

While this report challenges the current view that places PAF as an autonomic-specific synucleinopathy, other diagnoses and certain features of the case should be considered. Cases of autoimmune autonomic ganglionopathy (AAG) may mimic PAF [9]. Anti-nicotinic receptor antibodies were not detected in this patient. However, seronegative AAG may present with this clinical pattern, or the condition may be caused by other, yet to be fully identified, antibodies. While the catecholamine pattern and evidence of cardiac denervation counter the argument that this case is better classified as seronegative AAG rather than PAF, these tests are neither completely sensitive nor specific for AAG or PAF, respectively. An interesting aspect of this case is the normal QSART results throughout the disease course. In our PAF cases, sudomotor function is almost invariably affected, evidenced on thermoregulatory sweat test or QSART. However, normal QSART was in keeping with the patient's skin biopsy results, which showed only selective loss of sympathetic fibers to the arrector pili muscles and not sweat glands.

Could this case, therefore, represent a selective sympathetic ganglioneuropathy rather than PAF? And would that fit under the spectrum of seronegative AAG? The authors postulate that the patient's significant lifetime exposure to environmental agents could produce oxidative stress in catecholaminergic neurons that may have catalyzed his autonomic disorder. Then, perhaps seronegative AAG or a selective sympathetic neuropathy may be a more fitting diagnosis that PAF. Regardless, in the absence of a gold standard to diagnose either seronegative AAG or PAF, overlap may occur between the diagnoses.

The presence of dream-enactment behavior, suggestive of rapid eye movement (REM) behavior disorder, is in keeping with a diagnosis of PAF, however, in the reported case, this was not characterized with polysomnography and dream enactment behavior may be due to numerous causes. The presence of REM sleep behavior disorder is well recognized in PAF and is considered a manifestation of an evolving synucleinopathy [1].

So where do we go from here? Likely the largest group of PAF is due to a synucleinopathy. When we are able to reliably diagnose a synucleinopathy, either with cerebrospinal fluid or peripheral biomarkers, including identification of pathologic α-synuclein (as post-translational change or oligomers), we could segregate this group and identify predictors of conversion or non-conversion to MSA, PD or DLB. This approach is also important since cases destined to convert to MSA might be amenable to therapy at a treatable stage. This case highlights the question of how to classify those that may not "evolve". PAF in patients

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who live decades with solely their autonomic disease are perhaps a different etiologic and pathologic entity of a heterogeneous disease. How we approach and classify PAF should seek to create a “coherent heterogeneity.”

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