Critical review of pure autonomic failure raises awareness for early signs of Parkinson’s disease, Lewy body dementia, and Multiple System Atrophy

Pure autonomic failure (PAF) is both, a rare condition and a pathogenetic mystery, first described by Bradbury and Eggleston in 1925, as a syndrome characterized by orthostatic hypotension, fixed pulse rate, anhidrosis, erectile dysfunction, and constipation without motor features. The pathology of PAF is characterized by degeneration of peripheral autonomic neurons along with Alpha-synuclein–positive, Lewy body–like inclusions in sympathetic ganglia and widespread a-synuclein deposits in autonomic neurons, establishing PAF as a restricted, nonmotor form of the synucleinopathies.

Three observational studies published in 2017 and 2018, brought evidence that patients showing characteristics of PAF are not a distinct entity per se. The longitudinal data presented in these studies conversely suggested that a significant number of patients may gradually develop symptoms and signs of Multiple System Atrophy (MSA), Parkinson’s Disease (PD), or Lewy body dementia (DBL).

The first of these, presented data of a prospective cohort “The Natural History of Parkinson’s disease, Lewy body dementia, and Multiple System Atrophy” (PAF), incorporating that a significant number of patients may gradually develop symptoms and signs of MSA, PD, or DBL over five years or more than three years. They could confirm that the presence of subtle motor signs as slight gait imbalance or subtle tremor at the time of PAF diagnosis were risk factors for a phenoconversion to both, MSA or PD/DBL even if those findings at the time of study entry were too subtle to make a diagnosis of either parkinsonism or cerebellar dysfunction. Almost all patients who phenoconverted had RBD at the time of enrolment, 88 % had subtle motor deficits, and 53 % had olfactory loss.

Two further retrospective studies appeared to confirm the observations of Prof. Kaufman and his team: In their study “Pure autonomic failure – predictors of conversion to clinical CNS involvement”, Neurology 2017;88:1129–11, Professor Wolfgang Singer and his team followed a cohort of 79 patients with pure autonomic failure over more than three years. They could confirm that the presence of subtle motor signs as slight gait imbalance or subtle tremor at the time of PAF diagnosis were risk factors for a phenoconversion to both, MSA or PD/DBL even if those findings at the time of study entry were too subtle to make a diagnosis of either parkinsonism or cerebellar dysfunction. Almost all patients who phenoconverted had RBD at the time of enrolment, 88 % had subtle motor deficits, and 53 % had olfactory loss.

Patients staying with PAF showed low circulating NE at rest and a rise of more than 65 pg/dl as would be expected in a disease primarily affecting postganglionic autonom. Patients developing MSA were found to have supine plasma norepinephrine levels of > 110 pg/ml. In PAF with no CNS involvement, there was PET and SPECT evidence of vast postganglionic denervation of the heart which affects sympathetic and parasympathetic, vagal fibres. These are less common in MSA.
Another retrospective study was carried out by Professor Pietro Cortelli and his team: “The natural history of idiopathy autonomic failure”, Neurology 2018;00:1–10. doi:10.1212. Over a follow-up period of 7 years, clinical records including cardioautonomic data were collected from 50 patients with PAF (age 45 to 65 years) of which 16 patients developed CNS symptoms as RBD. As concluded by the main author Dr. Giulia Giannini, an early onset of urinary dysfunction, early onset of RBD, and Valsalva ratio ≥ 1.25 are variables which increase the probability of a phenoconversion of idiopathic autonomic failure to MSA, DLB, or PD. In contrast, patients retaining pure autonomic failure were typically found with fainting, diarrhoea, and a reduced heart rate variability at study entry.

From those three studies can be concluded that a considerable proportion of patients originally diagnosed with a rare condition of pure autonomic failure (PAF) may eventually convert to PD, DLB, or MSA. The observations summarized above warrant higher awareness for CNS symptoms in patients with autonomic failure. Diagnosis and follow-up examinations of patients with PAF should include a careful screening of sleep disorders, assessment of olfactory and cognitive functions as well as considering motor deficits and NE plasma levels. The observations suggest that in order to make accurate predictions and identify Alpha-synucleinopathies earlier the standards of examination need to be improved. The recognition of symptom patterns and dynamics over time may help predict a conversion towards PD, DLB, or MSA which potentially benefits future disease modifying strategies in the pre-motor/precognitive phase.