

## Autonomes Nervensystem: Neues aus Forschung und Praxis



### EAN Scientific News

## 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 (DLB).

The first of these, presented data of a prospective cohort "The Natural History of Pure Autonomic Failure: a U. S. Prospective Cohort", *Ann Neurol.* 2017 February; 81(2): 287–297. Professor Horacio Kaufman and collaborators had followed 74 patients between fifty and eighty years of age with a history of autonomic failure for five years on average. Whereas 49 patients stayed with PAF twenty-five of these were later diagnosed with PD, DLB, or MSA. They noted that all patients with PAF that went on to develop manifest PD or DLB had impaired olfactory function. All except for one had a probable REM-sleep behavioural disorder (RBD) at study entry. These symptoms are known to predict phenoconversion in premotor PD

cohorts. The careful review of their neurological examination showed subtle motor signs of CNS involvement at the entry visit already. These included mild bradykinesia, minimal hypomimia/reduced blinking, mildly reduced unilateral arm swing, and mild slowing/reduction in amplitude in rapid alternating movements. Symptoms as constipation and urinary symptoms were mild and occasional, and not requiring treatment. The diagnosis of PD/DLB was manifest 2 to 17 years after study entry.

The diagnosis of MSA was manifest around 2 to 8 years after study entry. At study entry, these patients were between 40 and 50 years of age suffering a symptomatic neurogenic orthostatic hypotension. They were significantly younger than those developing PD/DLB. Constipation and urinary symptoms were moderate or severe and required treatment. All patients diagnosed with MSA on follow-up had probable RBD at the time of entry. In contrast to those that developed PD or DLB, they all had preserved olfactory function. The increase in heart rate after 3-min of head-up tilt in phenoconverters to MSA was higher 12(3) bpm than in those converting to PD/DLB ( $p = 0.0001$ ). Moreover, supine resting plasma norepinephrine (NE) appeared to be higher 325 (163) pg/ml in MSA than in PD/DLB phenoconverters 118 (66) pg/ml. Those PAF patients who did neither convert to MSA, PD, or DLB were comparatively younger (mid-fifties) at study entry when compared to phenoconverters. They did not display CNS signs or symptoms over the time course of the study. A key feature of the non-converting subgroup seemed to be very low plasma norepinephrine levels. The authors concluded that the presence of RBD, olfactory loss, or subtle motor deficits should be con-

sidered as non-supportive features of PAF, because their presence indicate that CNS neurons are already involved in the disease process, and thus the failure not purely autonomic and is likely to progress. Hence, the diagnostic criteria of PAF should be modified to reflect these findings.

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/DLB 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 autonomic. 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  $\geq 1.25$  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 fol-

low-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.

#### IMPRESSUM

Prof. Dr. med. Christina Haubrich  
Leitungsteam  
Facharztzentrum Düsseldorf  
haubrich@fa-zd.de