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Very late-onset pure autonomic failure

Alessandra Fanciulli, MD PhD¹, Nadia Stefanova, MD PhD¹, Christoph Scherfler, MD¹, Patrizia Moser, MD², Klaus Seppi, MD¹, Elke R. Gizewski, MD^{3,4}, Irene Virgolini, MD⁵, Sylvia Boesch, MD¹, Werner Poewe, MD¹, and Gregor K. Wenning, MD PhD MSC¹

¹Department of Neurology – Innsbruck Medical University, Austria

²Pathology Institute - Innsbruck Medical University, Austria

³Department of Neuroradiology – Innsbruck Medical University, Austria

⁴Neuroimaging Research Core Facility - Innsbruck Medical University, Austria

⁵Department of Nuclear Medicine- Innsbruck Medical University, Austria

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Pure autonomic failure (PAF) is a rare disease characterized by neurogenic orthostatic hypotension, signs of more widespread autonomic failure, but no other neurological features¹. Disease onset is usually in the 5th-7th decade of life.

Corresponding Author: Univ.-Prof. Gregor K. Wenning, MD PhD MSC, Department of Neurology, Innsbruck Medical University, Anichstraße 35, A-6020 Innsbruck, Telefon: (+43) (0512) 504 818 11, Fax: (+43) (0512) 504 239 12, gregor.wenning@i-med.ac.at.

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Phosphorylated α -synuclein (p-syn) aggregates in peripheral sympathetic neurons are the neuropathological hallmark of PAF, and have been proposed as in-vivo biomarker to differentiate PAF from acquired autonomic neuropathies at skin biopsy².

Furthermore, neuronal p-syn aggregates have been documented in the substantia nigra and locus coeruleus of patients diagnosed in life with PAF³. Indeed, some patients presenting with PAF may progress into Parkinson's disease, dementia with Lewy bodies or multiple system atrophy over years⁴.

Here we report an unusual patient with exceptionally late-onset PAF, neuronal p-syn aggregates on abdominal skin biopsy and asymptomatic nigrostriatal dopaminergic denervation at neuroimaging.

During the past three years, an eighty-six years old female patient suffered from recurrent orthostatic syncope and supine hypertensive crises [supine systolic blood pressure (BP) >180 mmHg]. The patient also suffered from heat intolerance, constipation, recurrent urinary tract infections and nycturia. The patient recalled no nightmares or bed injuries, but the relatives reported frequent vocalisations during sleep.

Neurological examination showed no parkinsonism (MDS-UPDRS motor score: 3) or ataxia. Cognition was normal (29/30, Mini-Mental State Examination). Smell test revealed severe hyposmia (4/16, Sniffin'-Sticks identification test). Cardiovascular autonomic function tests showed moderate supine hypertension, coupled with severe neurogenic orthostatic hypotension (supine BP: 161/76, supine heart rate (HR) 66 bpm; BP after 3-minutes orthostatic challenge: -74/-28 mmHg, HR: -1). Parasympathetic cardiovascular autonomic function tests scored below age-matched norm values (HRmax/HRmin during active standing: 1.01; Valsalva ratio: 1.04). Physiological BP overshoots in the late phase-II and phase-IV of the Valsalva manoeuvre were also missing (BP late phase-II – early phase-II: -7/-25 mmHg; BP phase-IV – phase-I: -20/-35 mmHg), indicating cardiovascular sympathetic failure. ¹²³I-MIBG SPECT demonstrated severe cardiac sympathetic denervation (Fig. 1K). Uroflowmetry and bladder scan were normal. Laboratory screening for acquired autonomic neuropathies showed an increased serum and urinary κ/λ free light-chain ratio. However, nerve conduction studies reported no sensory-motor neuropathy and Congo-red staining of abdominal fat biopsy excluded light-chain amyloidosis, confirming the clinical diagnosis of PAF. p-syn staining of abdominal skin tissue disclosed p-syn aggregates in nerve fibres innervating the sweat glands (Fig. 1A to C).

Though brain MRI volumetry showed no specific atrophy pattern in our patient, loss of dorsolateral nigral hyperintensity was observed on 3.0 tesla susceptibility-weighted imaging (Fig. 1F). Such signal intensity change occurs in Parkinson's disease already at early stages (Fig. 1E) and may identify prodromal parkinsonism in idiopathic REM-sleep behaviour disorder⁵. Consistent with this assumption, ¹²³I-Fluopane CIT-SPECT also showed bilateral, symmetrical, putaminal dopaminergic denervation in our patient (Fig. 1I).

This is the first description of PAF with a disease onset above 80 years of age, broadening the clinical spectrum of this rare α -synucleinopathy. Biopsy findings in our patient support

previous reports, that neuronal p-syn aggregates at skin biopsy may be a useful in-vivo PAF biomarker².

Our patient had severe hyposmia. In the absence of polysomnography, it remains unclear, whether nocturnal vocalisations indicated a REM-sleep behaviour disorder. Both hyposmia and REM-sleep behaviour disorder have been reported in PAF before, suggest non-dopaminergic CNS involvement and have been recently described as risk factors for phenoconversion to Parkinson's disease or dementia with Lewy bodies^{6–8}.

Neuroimaging also showed asymptomatic nigrostriatal dopaminergic involvement in our patient, possibly indicating prodromal Parkinson's disease underlying this case of very late-onset PAF.

Future research will clarify how often pre-clinical nigrostriatal dopaminergic denervation occurs in PAF and whether loss of dorsolateral nigral hyperintensity on 3.0 tesla susceptibility-weighted imaging predicts development of overt parkinsonism.

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Figure 1.

Panel A to C: double immunofluorescence for phosphorylated α -synuclein (pSyn - pSyn#64Wako, visualized with Alexa 594-conjugated anti-mouse IgG, Life Technologies), and neurofilament H (NF-H - NF-H Millipore, visualized with Alexa 488-conjugated anti-rabbit IgG, Life Technologies) demonstrates pSyn deposits in NF-positive fibres innervating sweat glands of abdominal skin biopsy.

Susceptibility-weighted imaging on 3.0 tesla MR depicts an area of signal hyperintensity within the dorsolateral substantia nigra (arrows) corresponding to nigrosome 1 in a healthy

subject (D). No visible signal increase in the dorsolateral substantia nigra of a patient with Parkinson's disease (E), and our patient with PAF (F).

^{123}I -Fluopane CIT in a healthy subject (G), in a patient with Parkinson's disease (H), and in our patient with PAF (I).

^{123}I -MIBG cardiac SPECT in a healthy subject (J) and in our patient, showing severe sympathetic post-ganglionic denervation (K).