LETTER

Sympathetic cardiac denervation in Parkinson's disease and pure autonomic failure but not in multiple system atrophy

Three neurodegenerative diseases causing primary autonomic failure are pure autonomic failure (PAF), Parkinson's disease (PD), and multiple system atrophy (MSA). Differential diagnoses among these diseases are often difficult especially in early disease stage. For example, it may be difficult to determine whether a patient with parkinsonism and autonomic failure has PD or MSA. Recently, a decrease in myocardial uptake of meta-iodobenzylguanidine (MIBG), an analogue of norepinephrine, has been reported in PD but not in MSA using [^{123}I]MIBG myocardial scintigraphy.[1] This new imaging approach is thought to be of significance in the diagnosis and characterisation of akinetic rigid syndromes, especially PD. After that, we reported severe loss of cardiac sympathetic nerves in one patient with PD but not in one patient with MSA, which accounts for a difference in myocardial uptake of MIBG between PD and MSA.[2] However, our observation was based on the study in only a single patient of each disease. In this study, we immunohistochemically examined the heart tissues from four patients with PD, three patients with MSA, and one patient with PAF, and showed the involvement of postganglionic cardiac sympathetic nerves in PD and PAF but not in MSA.

Pathologically verified patients with PD (n=4; 70, 78, 81, and 82 years of age, three men and one woman), MSA (n=3; 55, 59, and 59 years of age, one man and two women), PAF (n=1; 81 years of age, one man), and control subjects (n=5; 55, 57, 72, 76, and 91 years of age, four men and one woman) participated in this study, which did not include the previous patients.[2] The clinical diagnosis of PAF was according to the criteria of The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. The duration of the illness was 2, 4.6, 8, and 10 years in PD, 5, 8, and 10 years in MSA, and 2 years in PAF. Three of four patients with PD, all the patients with MSA and the PAF patient had orthostatic hypotension (OH). [^{123}I]MIBG myocardial scintigraphy was examined for one patient with PD performed four years before the death and the patient with PAF performed one month before the death. Early phase of heart-mediastinum (H/M) ratio was 1.3 in PD and 1.38 in PAF (reference range: 1.94–2.57).[1] Postmortem examination revealed marked loss of neurons with numerous Lewy bodies in the substantia nigra, locus ceruleus, and dorsal vagal nucleus in the patients with PD. In the patients with MSA, marked loss of neurons in the pontine nuclei, cerebellar cortex, putamen, substantia nigra, inferior olive and intermediolateral nucleus of the spinal cord with widespread occurrence of glial cytoplasmic inclusions. No Lewy bodies were present. The patient with PAF showed prominent neuronal loss and a moderate number of Lewy bodies in the substantia nigra and locus ceruleus. Neuronal loss with gliosis was observed in the intermediolateral nucleus but there were no Lewy bodies observed in the intermediolateral nucleus, Onuf's nucleus, or Auerbach's plexus.

The anterior wall of the left ventricle from each subject was fixed with formalin for three to four weeks, and embedded in paraffin wax. The sections were stained with haematoxylin and eosin (H&E) or immunostained with a monoclonal antibody against tyrosine hydroxylase ((TH) Sigma, St Louis, MO; diluted 1:1000) by the avidin/biotin/peroxidase method with a Vectastain ABC kit (Vector, Burlingame, CA). On H&E staining, no abnormal findings were apparent in the nerve fibres both in the myocardium and epicardial space (fig 1 A, B, C, D) of each patient and control subjects. All the specimens from control subjects showed TH immunoreactive fibres both in the myocardium and epicardial space as well as those from all the patients with MSA. In contrast, TH immunoreactive fibres markedly decreased in number in the patients with PD and the patient with PAF (fig 1 G, H) compared with the MSA patients (fig 1 F) and the control subjects (fig 1 E).

Neurophysiological, neuropharmacological, and neuroendocrine evidence has revealed that postganglionic sympathetic nerves were involved in PAF and PD but not in MSA.[3] Pathologically, Iwanaga and colleagues reported Lewy bodies and α-synuclein positive neurites in the hearts from the patients with PD.[4] Recently, we reported a severe loss of cardiac sympathetic nerves in one patient with PD but not in one patient with MSA, which suggests the involvement of postganglionic sympathetic nerves in PD but not in MSA.[2] In the present study, TH immunoreactive nerve fibres markedly decreased in number in all the patients with PD, associated with or without OH, and the patient with PAF. In contrast, TH immunoreactive nerve fibres were well preserved in all the patients with MSA. These results confirm our previous observation that postganglionic cardiac sympathetic nerves are involved in PD but not in MSA, and show the involvement of cardiac sympathetic nerves in PAF. On the basis of these results and the previous report,[5] we infer that the involvement of postganglionic sympathetic nerves including the cardiac sympathetic nerves predominates in PD and PAF, but not in MSA, which accounts for a difference in myocardial uptake of MIBG among PD, PAF, and MSA.

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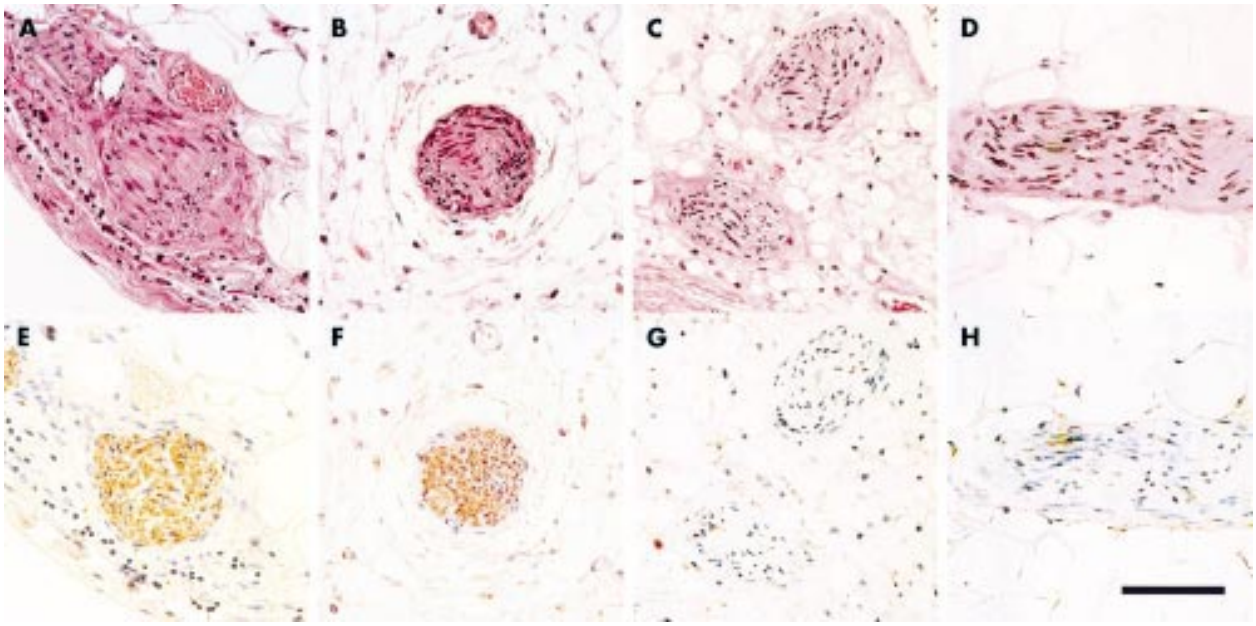

Figure 1 The figure shows H&E and TH staining of the nerve fibres in the epicardial space from the control subject (A, E), the patient with MSA (B, F), PD (C, G), and PAF (D, H), respectively. On H&E staining, no abnormal findings were apparent in each patient (A, B, C, D). However, TH immunoreactive nerve fibres in the patient with PD and PAF are markedly decreased (G and H) compared with the patient with MSA (F) and the control subject (E). The bar indicates 100 μm.

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References

1 **Orimo S**, Ozawa E, Nakade S, *et al*. ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. *J Neurol Neurosurg Psychiatr* 1999;**67**:189–94.
2 **Orimo S**, Ozawa E, Oka T, *et al*. Different histopathology accounting for a decrease in myocardial MIBG uptake in PD and MSA. *Neurology* 2001;**57**:1140–1.
3 **Mathias CJ**, Polinsky RJ. Separating the primary autonomic failure syndromes, multiple system atrophy, and pure autonomic failure from Parkinson's disease. In: Stern GM, ed. *Advances in neurology*. Philadelphia: Lippincott Williams and Wilkins, 1999:353–61.
4 **Iwanaga K**, Wakabayashi K, Yoshimoto M, *et al*. Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental Lewy body diseases. *Neurology* 1999;**52**:1269–71.
5 **Wakabayashi K**, Takahashi H, Ohama E, *et al*. Lewy bodies in the visceral autonomic nervous system in Parkinson's disease. In: Narabayashi H, Nagatsu N, Yanagisawa N, *et al*, eds. *Advances in neurology*. New York: Lippincott-Raven, 1993:609–12.

An adult Japanese Sanfilippo A patient with novel compound heterozygous S347F and D444G mutations in the sulphamidase gene

Sanfilippo A is a neurodegenerative disease characterised by progressive dementia, sleep disturbance, developmental delay, hyperactivity, and aggressive behaviour. Sanfilippo A is inherited as an autosomal recessive disease caused by a defect of the lysosomal enzyme sulphamidase (N-sulphoglucosamine sulphohydrolase, SGSH, EC 3.10.1.1). Failure of the degradative effect of sulphamidase is thought to cause lysosomal accumulation of heparan sulphate, leading to neuronal dysfunction. Developmental abnormality is often noticed at 2 or 3 years of age and severe neurological deterioration occurs in most patients by 6 to 10 years of age.[1] The average age at death is 13 years.[2] The comparatively mild somatic manifestations often cause a delay in the diagnosis.[1 2] The gene encoding Sanfilippo A has been cloned.[3] We now report on a Japanese Sanfilippo A patient.

A 26 year old patient had no recognisable developmental abnormality until the age of 4 years, when he had mild language disability without motor dysfunction. Mild ventricular enlargement and brain atrophy were found at the age of 12 years. Despite his language disability, motor function was well retained even in high school. Hyperactivity and irritability appeared at the age of 17 years, and mental deterioration ensued. Simple conversation was retained until the age of 24 years. The diagnosis was made then with the demonstration of increased excretion of heparan sulphate in urine and decreased sulphamidase activity in cultured fibroblasts (not detected; control 3.2–7.2 nmol/h/mg). His older brother had a mild language disability and died as a result of an accident at the age of 19 years. There was no family history of consanguinity.

The patient was 164 cm in height, and weighed 50.4 kg. There was no recognisable pattern of malformation. His hair was stiff and coarse. No corneal opacities were found. Facial expression was poor, and affect was flattened. He had no meaningful expressive language. Visual pursuit was poor and frequently discontinued. Agitation could be induced by tactile or visual stimuli. Touching his limbs and trunk induced coordinated repetitive coarse movements such as holding up both arms and legs. There was no obvious weakness found, but ankle contractures render him wheelchair bound. Deep tendon reflexes were normal.

A magnetic resonance imaging examination of the brain revealed thinning of the corpus callosum, ventricular enlargement and widening of the sulci. Cribriform changes (small cystic lesions) were found in the frontal lobe.

Genomic DNA was extracted from peripheral blood leucocytes using the Capture Column kit (Gentra systems, MN). The sulphamidase gene consists of eight exons. The primer pairs used to amplify the exons by polymerase chain reaction (PCR) were described by Weber *et al*.[4] Sequencing was done using an ABI 377 automated fluorescence sequencer (Perkin Elmer, Foster City, CA). Numbering of amino acids and nucleotides is according to Scott *et al*.[3]

To determine the possibility of mutations in the sulphamidase gene, PCR was done on the genomic DNA of the patient. We sequenced all the coding regions and the sequence obtained showed two heterozygous nucleotide substitutions: a C to T at the position 1052 (S347F) and an A to G transition at the position 1343 (D444G), and one homozygous polymorphism: a G to A transition at the position 1367 (R456H). The patient's mother had a single heterozygous nucleotide substitution: a C to T transition at the position 1052 (S347F), while his father had a heterozygous nucleotide substitution: an A to G transition at the position 1343 (D444G) (fig 1).

This is the first report of a genetically identified Japanese Sanfilippo A patient. The gene encoding sulphamidase spans about 11 kb,

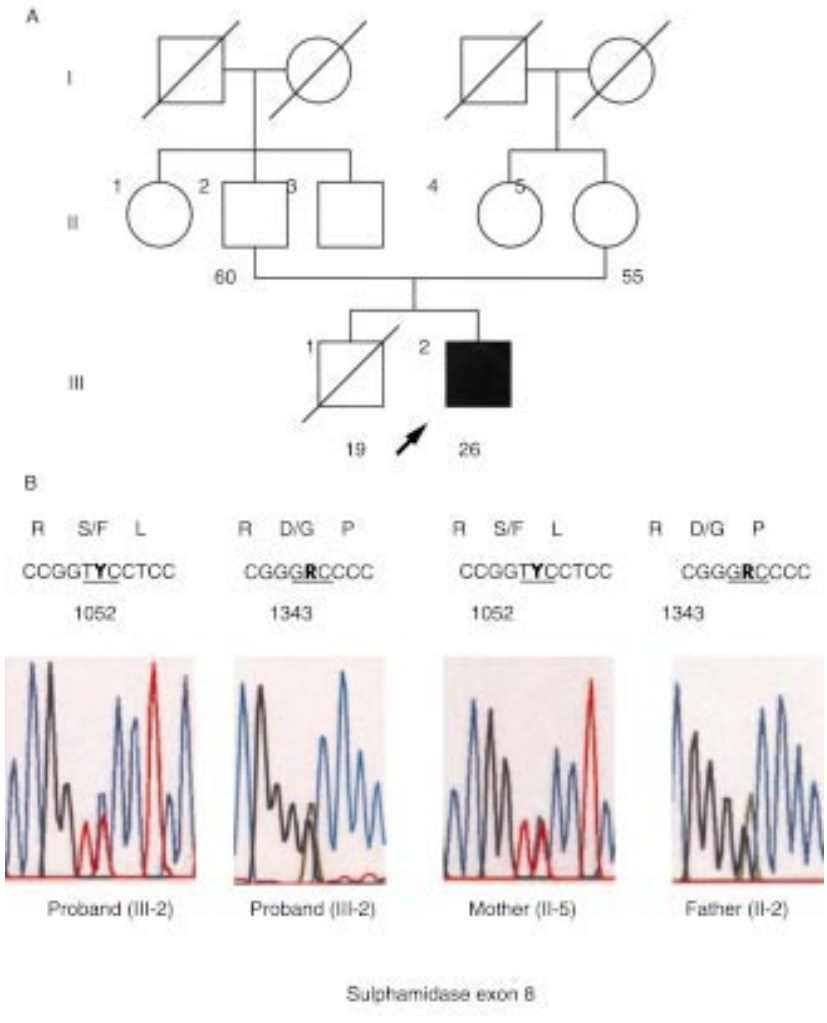

Figure 1 (A) Pedigree of the patient. The arrow represents the proband. (B) Direct sequencing of polymerase chain reaction amplified products from exon 8 of sulphamidase gene. Bold letters indicate the mutation site. R indicates nucleotides A and G, Y indicates nucleotides C and T.