

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 metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, has been reported in PD but not in MSA using [¹²³I]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). [¹²³I]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,³ 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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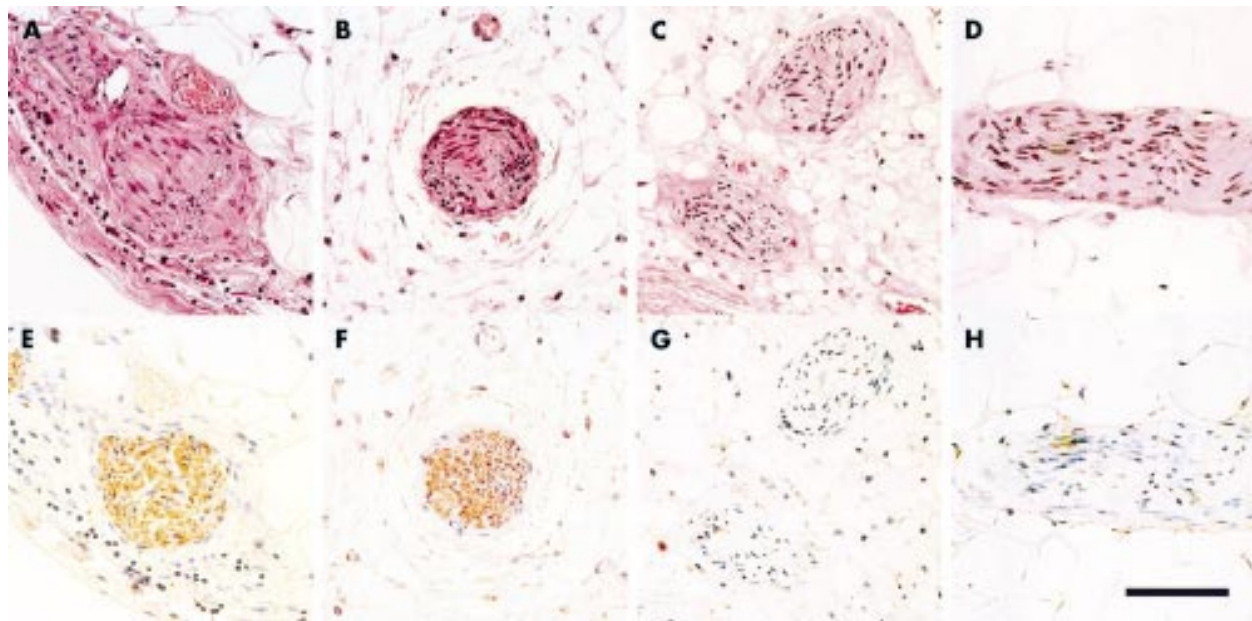


Figure 1 The figure shows H&E and TH staining of the nerve fibres in the epicardial space from the control subject (A, E), the patient with MSA (B, F), PD (C, G), and PAF (D, H), respectively. On H&E staining, no abnormal findings were apparent in each patient (A, B, C, D). However, TH immunoreactive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

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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.*⁵

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,

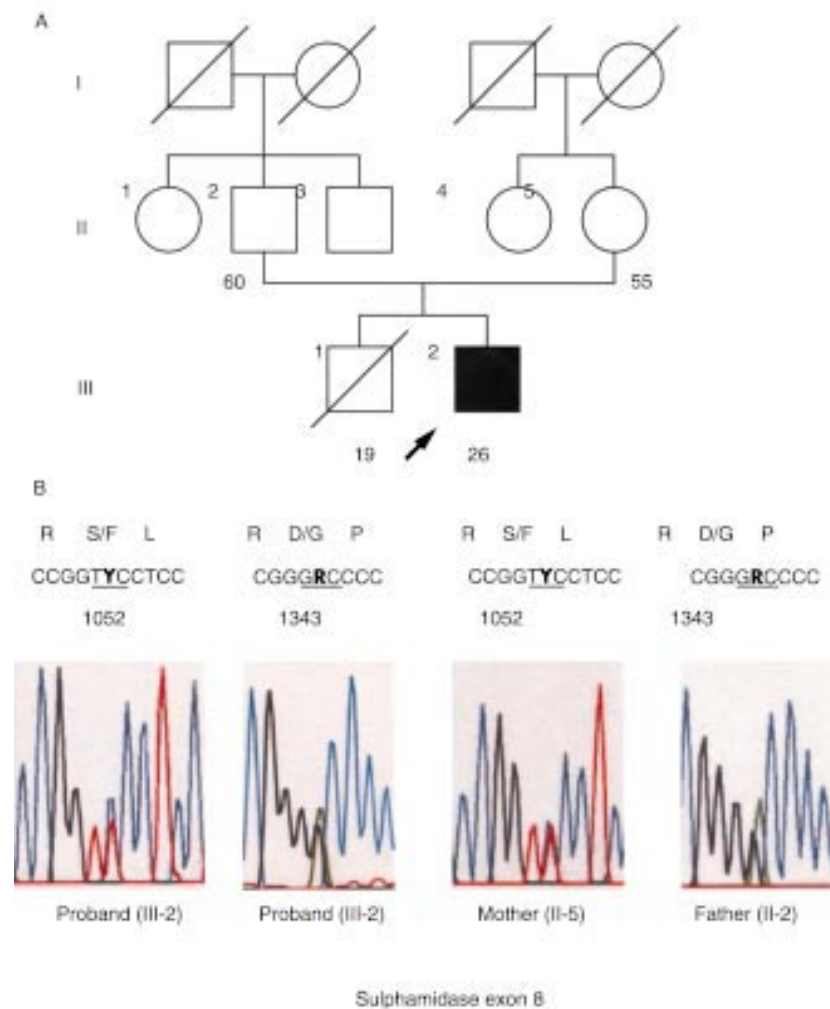


Figure 1 (A) Pedigree of the patient. The arrow represents the proband. (B) Direct sequencing of polymerase chain reaction amplified products from exon 8 of sulphamidase gene. Bold letters indicate the mutation site. R indicates nucleotides A and G, Y indicates nucleotides C and T.

includes 8 exons, and is localised to chromosome 17q25.3.³ We found two novel mutations (S347F, TCC to TTC and D444G, GAC to GGC) in exon 8. The sulphamidase shares few commonly conserved sites toward the C terminus, and the conserved sites are relatively scarce in exon 7 and exon 8.⁴ The serine (S) residue at position 347 and the aspartic acid (D) residue at position 444 are located on sparsely distributed conserved sites among sulphatase families under the superimposition of the sequence of protein sulphatases. Polymorphisms were not reported at these two sites (1052 C to T, and 1343 A to G). These two mutational sites are conserved in the evolutionary process and obey the rule of Mendelian inheritance. Therefore, these mutations were predicted to cause disease.

The clinical course of the patient in this report was relatively slow. In reporting 73 patients with Sanfilippo syndrome, van de Kamp *et al* found that Sanfilippo A had a more severe phenotype than Sanfilippo B and C.² The average age of death of Sanfilippo A was 13 years (range 6–25) and the age range of the living patients was 5–26 years.² Motor functions of the patient in this report were well retained and language abilities remained until the age of 24 years. Significant clinical heterogeneity has been known in Sanfilippo syndrome (include Sanfilippo A).² Mild somatic abnormalities and false negative results of urine tests in the Sanfilippo A patients often cause a delay in diagnosis.¹ Therefore, it is important to investigate the genetic background in patients with the milder form of Sanfilippo A syndrome. The residual function derived from the better allele may be critical for enzyme activity in an autosomal recessive disease. Large scale statistical analysis of Sanfilippo A patients has not been performed in Japan. Date and coworkers reported long term surviving Japanese siblings (32 and 34 year old brothers) with enzymatically diagnosed Sanfilippo A.⁵ Patients with the clinically milder course may predominate in Japan. Further study is needed for evaluating mutational predominance and its clinical relevance in Japanese Sanfilippo A patients. Competing interests: none declared.

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Parkinson's disease: neurosurgery at an earlier stage?

Bilateral high frequency stimulation of the subthalamic nucleus (STN) is an alternative treatment for advanced forms of levodopa-responsive Parkinson's disease (PD) with severe motor complications.¹ Most patients so far treated in this way had their disease for an average of 15 years,² no longer worked, were socially isolated and dependent on their families. As this neurosurgical treatment remarkably improves parkinsonian motor disability and levodopa induced dyskinesias, we wondered whether operating earlier during the course of the disease would enable patients to maintain their previous social and professional status. A retrospective analysis of 41 successive severely disabled PD patients operated in our department³ showed that four of them, who had disease duration of less than 10 years, were allowed to still maintain their professional activity after neurosurgery.

Case 1

A 47 year old man, restaurateur with two dependent children, had had PD for five years. Levodopa induced dyskinesias were so severe that he was no longer able to cope with his managerial functions and feared bankruptcy. Six months after neurosurgery, parkinsonian motor disability, daily doses of levodopa, and severity of levodopa induced motor complications decreased by 97%, 87%, and 100%, respectively. The patient has sold his business but has resumed his professional activity in another establishment.

Case 2

A 48 year old woman, single without children, had had PD for five years. The response to levodopa treatment was excellent apart from disabling levodopa related motor complications.

She was the assistant director of a jewellery shop and had increasing difficulties performing her job. She was frequently on sick leave, and for this reason, was about to be made redundant. Bilateral stimulation of the STN reduced her motor handicap, daily doses of levodopa, and levodopa induced motor complications by 95%, 93%, and 90%, respectively. Nine months after the operation, she was again working full time.

Case 3

A 46 year old woman, divorcee with two dependent children, had had severe PD for nine years. She was an emergency room nurse, but had been on sick leave for two years

and expected to be let go for reasons of invalidity. The operation reduced her motor handicap, daily doses of levodopa, and levodopa induced motor complications by 87%, 76%, and 84%, respectively. Four months after the operation, she went back to work half time in the outpatient clinic of the department of medicine.

Case 4

A 50 year old woman, married with one child, had had severe PD for five years. She was a lawyer and feared being unable to continue to exercise her profession. Nine months after neurosurgery, her motor handicap, daily doses of levodopa, and levodopa induced motor complications were reduced by 84%, 80%, and 75%, respectively. She is successfully pursuing her career.

These findings suggest that bilateral high frequency stimulation of the STN, when performed sufficiently early in the evolution of PD, can prevent the motor handicap and adverse reactions of levodopa from interfering with socio-professional integration and family life. Although this is an open label observation of select PD patients reported in the absence of long term follow up, we wonder whether one should not give PD patients a chance for a normal life, when otherwise they are certain to lose their job and their autonomy, even with optimised antiparkinsonian medications. We propose that a controlled study should be performed to demonstrate the validity and the economical consequences of this proposition. Such a decision needs to be balanced by taking into consideration the long waiting lists in the centres performing such surgery and the risks associated with neurosurgery.

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