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. 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. 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), 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. 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). 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) and 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 subject (fig 1 E). Neurpathologically, Iwanaga and colleagues reported Lewy bodies and α-synuclein positive neurites in the hearts from the patients with PD. 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. In the present study, 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, 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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The Ueda Memorial Trust Fund For Research of

Funding: this work is supported by a grant from

Developmental abnormality is often noticed
to cause lysosomal accumulation of heparan sul-
phate 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 fre-
quently 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 cor-
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tal lobe.

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

Sanfilippo A is a neurodegenerative disease
classified by progressive dementia, sleep
disturbance, developmental delay, hyperactiv-
ity, and aggressive behaviour. Sanfilippo A is
inherited as an autosomal recessive disease
caused by a defect of the lysosomal enzyme
sulphamidase (N-sulphoglucosaminyl sulpho-
carboxylase, 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.5 The average age at death is 13
years.4 The comparatively mild somatic mani-
festations often cause a delay in the
diagnosis.4 5 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 dis-
ability, 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 demon-
stration of increased excretion of heparan sul-
phate in urine and decreased sulphamidase
activity in cultured fibroblasts (not detected;
control 3.2–7.2 nmol/h/mg). His older brother
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includes 8 exons, and is localised to chromosome 17q23.  

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.  

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. 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. 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). Mild somatic abnormalities and false negative results of urine tests in the Sanfilippo A patients often cause a delay in diagnosis. 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 syndrome, van de Kamp et al found that four of 73 patients with Sanfilippo syndrome, van de Kamp et al reported 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 department 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. Levodopa induced dyskinesias were so severe that she was frequently on sick leave, shopping and had increasing difficulties performing her job. She was frequently on sick leave, shopping and had increasing difficulties performing her job. 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 manager 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 subthalamic nucleus (STN) is an alternative treatment for advanced forms of levodopa-responsive Parkinson’s disease (PD) with severe motor complications.  

References  