SHORT REPORT

Pure autonomic failure: a new case with clinical, biochemical, and necropsy data

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Abstract

Postmortem examination of a patient with pure autonomic failure showed loss of intermediolateral column cells and of sympathetic ganglionic neurons; there were Lewy bodies in sympathetic neurons. No neuronal loss or Lewy bodies were seen in pigmented brainstem nuclei. This case indicates that pure autonomic failure can occur in the absence of presymptomatic Parkinson's disease. Furthermore, it supports the view that in pure autonomic failure the lesion is more distal than in autonomic failure associated with multiple system atrophy.

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In primary autonomic failure the dysautonomia results from an unexplained selective neuronal degeneration. In virtually all patients studied at postmortem, severe loss of intermediolateral column cells is noted.¹ This may occur in association with two degenerative diseases of the central nervous system: Parkinson's disease and multiple system atrophy. It also may occur in a pure, isolated form without other neurological signs: this is called pure autonomic failure.

Although Oppenheimer² showed a strong correlation between autonomic failure and intermediolateral column cell loss, some authors are not convinced that a central lesion in pure autonomic failure is proved because only few cases of pure autonomic failure came to postmortem examination. Moreover, owing to biochemical, pharmacological, and electrophysiological studies, pure autonomic failure is considered a primary disorder of postganglionic sympathetic efferent neurons. We present a new case of pure autonomic failure with clinical, biochemical, and necropsy data.

Case report

A 64 year old man was admitted to hospital in October 1990 because of transient ischaemic attacks related to abrupt changes in position. From 1972 to 1983 he was treated for hypertension with diuretics, pindolol, and lisinopril; he never took guanethidine. In 1983 he felt faint on standing and became impotent. There was progressive loss of sweating over the entire body. In December of that year, orthostatic hypotension was documented for the first time: blood pressure was 300/120

mmHg supine and 90/60 mmHg on standing. By the age of 59, he was incapacitated by orthostatism: he developed gradual fading of consciousness over a few minutes while standing or walking. Three years later postprandial syncope became frequent. Bowel and bladder control were not affected.

On admission, supine blood pressure was 270/100 mmHg; this fell to 230/80 mmHg on standing; his pulse rate was fixed at 61 beats per minute. Neurological evaluation was normal: there was no clinical evidence of pyramidal, extrapyramidal, or cerebellar disease. There were no signs of peripheral nerve involvement. CT of the brain was normal. Analysis of CSF concentrations of homovanillic acid was not done.

We studied the patient on an electrically powered tilt-table. He rested in the supine position for 30 minutes before tilting. Blood pressure was automatically measured by an intra-arterial cannula; a one lead ECG was recorded continuously. Plasma noradrenaline concentrations were obtained at 0°, 30°, 60°, and 90° head up tilt. The patient was kept for five minutes in each tilted position. We noted a postural drop in systolic blood pressure of 100 mmHg and in diastolic pressure of 30 mmHg. Postural symptoms occurred two to five minutes after 90° head up tilt. The ECG showed a fixed heart rate of 61 beats/min. Noradrenaline concentrations were very low in the supine position (160 pmol/l; normal range 790 to 3140 pmol/l) and failed to increase after five minutes of head up tilting.

No Valsalva manoeuvre was undertaken, but a cold pressor test was performed. Before and during the test, we measured the blood pressure, the pulse rate, and the noradrenaline concentration. After immersion of the left hand in ice cold water for one minute, the three variables failed to increase. Heart rate variation was reduced to 5 beats/min. The sympathetic skin response was absent.

Treatment with 9- α -fluorohydrocortisone (0.1 mg daily) was started. The patient was advised to sleep in the head up position. Orthostatic hypotension improved: the patient could walk again and could shop independently. Fluorohydrocortisone was discontinued after three months because of threatening heart failure. Two months later, the patient was admitted to hospital because of a left intracerebral haematoma which led to death after two days.

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Figure 1 Normally pigmented neurons in the substantia nigra. Slight spongiosis due to uncus herniation (haematoxylin-eosin, originally $\times 152$).

Figure 2 Severe neuronal depletion of intermediolateral column cells (dotted outlines at the right) at sixth thoracic level (cresyl violet, originally $\times 40$).

Neuropathological findings

General necropsy examination showed severe generalised atherosclerosis, left ventricle hypertrophy, and bilateral pulmonary emphysema. The left hemisphere of the brain was very swollen with signs of uncus herniation. Sectioning of the brain showed a large haematoma involving the internal capsule and the basal ganglia of the left hemisphere. The basal ganglia on the right appeared normal.

On microscopical examination, the substantia nigra and the locus coeruleus were well pigmented. The substantia nigra showed some acute spongiosis and neuronal swelling probably due to uncus herniation, but no significant neuronal rarefaction (fig 1). No Lewy bodies could be detected on multiple sections

of the substantia nigra or the locus coeruleus, neither with routine haematoxylin-eosin staining nor with immunohistological staining with antibodies against ubiquitin. No cell loss was detected with routine histological methods in the inferior olivary nuclei, in the pontine nuclei, or in the cerebellar nuclei. A Bielschowsky silver stain and staining with antibodies against τ -protein did not reveal intracytoplasmic glial inclusions in the striatonigral system, in the olivopontocerebellar system, or in the spinal cord.

The intermediolateral column was examined at four levels (T2, T6, T8, T11) according to Oppenheimer.² From each level, nine to 11 paraffin sections 20 μ m thick were stained with cresyl violet (Nissl method). Neurons were counted in the lateral horn on both sides. The mean cell count was 5.7 (SD 0.7) at T2 (control 12.2 (0.6)), 5.1 (1.3) at T6 (control 8.3 (0.4)), 4.5 (1.2) at T8, and 4.9 (1.2) at T11 (control 6.8 (0.4)). Thus there was a significant depletion of neurons in the intermediolateral column (fig 2).

Examination of lumbar paravertebral sympathetic ganglia revealed a striking loss of nerve cells, neuronal degeneration, and numerous intraneuronal eosinophilic Lewy bodies. The Lewy bodies stained positively with antibodies against ubiquitin (fig 3).

Discussion

Graham and Oppenheimer³ first distinguished between two types of primary autonomic failure: the first type occurring in cases of multiple system atrophy and the other type presenting as a clinically pure autonomic failure, sometimes associated with Parkinson's disease. In multiple system atrophy, there is degeneration of striatum, pigmented nuclei, pontine nuclei, inferior olives, cerebellar Purkinje cells, dorsal vagal nuclei, and vestibular nuclei.^{4,5} Intracytoplasmic argyrophilic oligodendroglial inclusions are present in those areas.⁶ In pure autonomic failure, neuronal loss is confined to the pigmented brainstem nuclei and the sympathetic ganglia; Lewy bodies are found in these structures.¹ In both types the intermediolateral column cells are affected.

Our case fully conforms to the clinical description of pure autonomic failure in other publications.⁷ It includes severe orthostatic hypotension without pulse acceleration leading to fainting, anhidrosis, impotence, and postprandial syncopal episodes. Autonomic failure gradually worsened over eight years. No other neurological signs appeared. There was no clinical evidence of a secondary form of autonomic failure. Function tests confirmed a loss of parasympathetic as well as sympathetic autonomic functions, making the possibility of a dopamine- β -hydroxylase deficiency⁸ very unlikely. The low resting plasma concentration of noradrenaline and the lack of increase with postural change indicated a disorder of postganglionic efferent neurons.^{9,10}

The neuropathological findings of our case differ from earlier published cases: indeed, all patients with pure autonomic failure who were examined postmortem had Lewy bodies in

Figure 3 (A) Neuronal degeneration with presence of Lewy body (arrows) in sympathetic ganglion (haematoxylin-eosin, originally $\times 712$). (B) Detail of neuron with focus on Lewy body (arrow) immunostained with antibodies against ubiquitin (originally $\times 540$).

their pigmented brainstem nuclei, sometimes associated with neuronal loss.^{1,11} Different cases were reported in which parkinsonian signs eventually developed some years after autonomic failure.^{12,13} Johnson *et al*¹⁴ described a patient who developed autonomic failure and died without evidence of Parkinson's disease four years later. Lewy bodies were present in the substantia nigra, in the intermediolateral columns, and in cervical and thoracic sympathetic ganglia. Similar patients with "pure" autonomic failure were reported; in all cases neuronal loss or Lewy bodies were noted in the pigmented brainstem nuclei.^{2,15,16} These reports therefore suggested a link between pure autonomic failure and presymptomatic Parkinson's disease.

In our case, there was no evidence of multiple system atrophy. Neither did we find any cell loss, neuronal degeneration, or Lewy bodies in pigmented brainstem nuclei. The pathological alterations were limited to intermediolateral column cells and sympathetic ganglia. Intermediolateral column cells were appreciably depleted. In the sympathetic ganglia, there was a pronounced loss of neurons and neuronal degeneration associated with Lewy bodies.

To our knowledge, this is the first published case of pure autonomic failure without alterations in pigmented brainstem nuclei. As the disease progressed over more than eight years, Parkinson's disease, even in a presymptomatic stage, can be excluded. Our case points to histological differences between autonomic failure in (preclinical) Parkinson's disease and pure autonomic failure: in the first there is depigmentation and neuronal loss in pigmented brainstem nuclei associated with generalised Lewy bodies; in the second there is lack of depigmentation and neuronal loss in pigmented nuclei and Lewy bodies are restricted to the autonomic nervous system. Our findings lend support to the clinical classification of primary autonomic failure into three groups as proposed by Bannister⁷: (a) pure autonomic failure, (b) autonomic failure associated with Parkinson's disease, and (c) autonomic failure in multiple system atrophy.

Which lesions are responsible for autonomic failure? Oppenheimer² showed that a strong correlation existed between autonomic failure and intermediolateral column cell loss. This does not mean that autonomic failure is directly due to loss of these cells. Moreover, some authors are not convinced that a central lesion in pure autonomic failure is proved because only very few cases of pure autonomic failure were examined after death. In five of six cases of autonomic failure with Parkinson's disease, Rajput and Rozdilsky¹³ reported considerable neuronal loss and degeneration in sympathetic ganglia, as opposed to minimal loss of neurons in the intermediolateral columns.

Sympathetic ganglia are not often sampled at necropsy for histological examination. Therefore, the incidence and significance of lesions of sympathetic ganglia might have been overlooked. Matthews¹⁷ made a histo-

pathological examination of sympathetic ganglia from subjects with multiple system atrophy or pure autonomic failure and from subjects dying of other causes. Her study pointed to a clear difference in ganglionic pathology between both types of primary autonomic failure: in multiple system atrophy the sympathetic ganglia are relatively intact, whereas in pure autonomic failure there is loss of ganglionic neurons. The hypothesis that the lesions in pure autonomic failure are more distal accords with evidence from biochemical, pharmacological, and microneurographical studies.^{10,18}

Our case provides further evidence for a loss of both intermediolateral column cells and ganglionic neurons in pure autonomic failure. It supports the view that in pure autonomic failure the lesion is more distal than in autonomic failure associated with multiple system atrophy.

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