Letters to the Editor


Pure autonomic failure with motor neuron disease: report of a clinical study and postmortem examination of a patient

From clinical and pathological viewpoints, primary chronic autonomic failure is divided into three types: pure autonomic failure without other neurological conditions, autonomic failure with multiple system atrophy, and autonomic failure with Parkinson's disease. In pure autonomic failure, the main pathological findings were neuronal loss in the intermediolateral columns of the spinal cord and the occurrence of eosinophilic bodies in the sympathetic ganglia. Furthermore, Lewy bodies in the substantia nigra or locus coeruleus were also described. Because the necropsied cases of pure autonomic failure always showed Lewy bodies in the brainstem, it has been considered as an extreme variant of autonomic failure with Parkinson's disease. Our patient was a man with pure autonomic failure whose prominent symptoms were ataxic gait hypotension, and who showed the neuropathological changes reported in pure autonomic failure as well as those in a familial form of motor neuron disease.

A 78 year old man had claimed dizziness on standing for the past five years. At the age of 76, he had noted frank syncope which gradually increased in frequency. No other symptoms had been experienced until the last year, when he was admitted to our hospital. He had had chronic bronchitis for the past 10 years. There was no family history suggesting neuromuscular diseases. On admission, physical examination disclosed severe orthostatic hypotension and diffuse mild weakness of the limb muscles. Muscle tone and deep tendon reflexes were normal. Pathological reflexes, muscle atrophy, fasciculation, cerebellar ataxia, and sensory disturbance were not seen.

Laboratory studies of blood, urine, and CSF were within normal limits. A chest radiograph showed mild reticular changes in the lower fields of the lungs. Cranial CT, MRI, and ECG showed no abnormal findings. Needle EMG and nerve conduction studies were not performed. A blood pressure of 106/30 mm Hg in the supine position decreased to 50/30 mm Hg on head up tilt, with no change in the heart rate (58 bpm). There was no postural change in serum noradrenaline concentration (0.03 ng/ml (controls: 0.05-0.40 ng/ml)), although plasma renin activity and serum arginine vasopressin were appropriately increased. The cold pressor test caused a decrease in blood pressure, from 104/54 to 90/50 mm Hg. An exaggerated increase in blood pressure (from 100/40 to 186/100 mm Hg) was obtained after treatment with intravenous noradrenaline. The coefficient of variation of the mean R-R interval of the ECG was reduced to 0.39% (controls > 1.14%). Intravenous infusion of atropine induced no change in heart rate. The phase IV overshoot of blood pressure after a Valsalva manoeuvre was absent. The pupillary responses to the instillations of both 5% tyramine and 1:25% noradrenaline were normal. The Schürmer test showed decreased laceration. Volume of residual urine was 10 ml and cystometry was normal. The patient died of subacute interstitial pneumonia eight months after admission.

His brain weighed 1020 g. Macroscopic findings were not remarkable. Paraffin sections were stained with haematoxylin-eosin, cresyl violet/Luxol fast blue, and silver impregnation (Bodian stain, Gallyas stain). Immunohistochemical staining with the avidin-biotin peroxidase procedure for identification of ubiquitin and phosphorylated high molecular weight neurofilaments was carried out. Multiple sections from various cortical areas including the precentral gyrus were unremarkable. No neuronal inclusions could be identified. Neurotic plaques were absent. Neurofibrillary tangles were noted in the hippocampus. The striatum, globus pallidus, thalamus, subthalamic nucleus, and hypothalamic nucleus appeared normal. The cerebral white matter was unremarkable. No glial cytoplasmic inclusions were noticed. The substantia nigra and locus coeruleus were examined at two and four different levels, respectively. Several sections from each level were stained with haematoxylin-eosin and immunohistologically with antibodies against ubiquitin and neither neuronal loss nor Lewy bodies were detected. The oculomotor and Edinger-Westphal nuclei showed normal appearance. Mild neuronal loss and gliosis had occurred in the facial and hypoglossal nuclei. In both nuclei, chromatolytic neurons and intracytoplasmic Lewy body-like hyaline inclusions were occasionally noted. Almost total neuronal loss was found in the dorsal motor nuclei of the vagal nerve (fig 1). The accessory cuneate nuclei showed mild neuronal loss. The reticular formation in the medulla exhibited mild astrogliosis as well as a few hyaline inclusions. The red nuclei, raphe nuclei, pontine nuclei, inferior olivary nuclei, and pyramids were not affected. In the cerebellum, Parkinje cells were slightly decreased in number, and the dentate nucleus showed a mild degree of grumose degeneration. There was no noticeable myelin pallor of the cerebellar white matter. In the spinal cord, there was severe loss of sympathetic neurons of the intermediolateral columns. This was accompanied by moderate loss of anterior horn motor neurons throughout the thoracic and lumbar cord. Clarke's columns also showed neuronal loss (fig 2A). In the anterior horns, chromatolytic neurons, spheroids, intraneuronal conglomerates, and hyaline inclusions were occasionally encountered. Swollen cord-like axons were seen in the intramedullary portion of the spinal anterior root. Astrogliosis and a few hyaline inclusions were also noted in the intermediate zone of the spinal cord. No pathological findings were recognised in Omüt's nucleus.

Figure 1 Dorsal vagal nucleus (dotted outlines) showing severe neuronal loss (haematoxylin-eosin × 120).
system respectively. Thus the whole clinical feature of the patient could be diagnosed as pure autonomic failure, which was chiefly concerned the cardiovascular system. The main pathological changes were found in the dorsal vagal nuclei and intermediolateral columns, which were considered to be the neuroanatomical system with the predominant involvement of the degenerative process. Along with the existence of eosinophilic bodies in the sympathetic ganglia, these findings were similar to those described in pure autonomic failure. By contrast with the previously reported cases, this patient showed the absence of neuronal loss or Lewy bodies in the substantia nigra and locus coeruleus. This suggests that pure autonomic failure could be recognised as a clinicopathological entity separated from multiple system atrophy or Parkinson’s disease.

Although motor neuron disease does not usually coexist with autonomic failure, our patient exhibited loss of anterior horn cells and pyramidal tract degeneration. In addition, we found symmetric patches of myelin loss in the posterior columns, degeneration in the spino-cerebellar tracts, and loss of cells from Clarke’s columns. This type of distribution is similar to that reported in cases of a familial form of motor neuron disease. Furthermore, Lewy body-like hyaline inclusions and swollen cord-like axons, which were both noted in our patient, have often been described in these familial cases. Whether a familial form of motor neuron disease constitutes a distinct disease entity or not, our patient shares its characteristics. The autonomic nervous system may be affected in motor neuron disease, with—for example, a mild degree of neuronal loss in the intermediolateral columns. However, out patient showed the obvious neurodegenerative changes reported in pure autonomic failure as well as those described in a familial form of motor neuron disease. Therefore this case shows an unusual constellation of pure autonomic failure and motor neuron disease.

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Glutaric aciduria type 1 in adulthood

Glutaric aciduria type 1 (GA-1) is an autosomal recessive disorder caused by deficiency of the mitochondrial enzyme glutaryl CoA dehydrogenase, which oxidises and carboxylates glutaryl CoA, an intermediate step in the metabolism of lysine and tryptophan. The onset of clinical manifestations is usually within the first year of life with an acute encephalopathic illness, often triggered by infection. A severe dystonic-dyskinetic syndrome is usually present in the majority of patients, but others are less severely affected and asymptomatic cases have been described. It is a rare condition with only about 100 cases reported in the medical literature since its original description in 1975. However, it has been suggested that GA-1 is underdiagnosed and may exist undetected in populations of children and adults labelled as having cerebral palsy. We report a patient with GA-1 in whom the diagnosis was made at the age of 50 years when she was referred for reassessment of chronic neurological disability.

The patient, the product of a full term normal delivery and there were no problems in the neonatal period. Motor development was mildly delayed, and she did not start to walk until the age of 18 months when she was noted to have her right leg. At the age of 7 years she was admitted to hospital with a "paralytic illness". She remained in hospital for four months and at the time of discharge required callipers to walk. Her manual dexterity was poor and her speech was slurred. These neurological disorders subsequently remained stable. At the age of 12 a right subternal fusion was performed, and eight years later the left femur was shortened. She was able to complete her education at a normal school and then worked for 10 years in a factory before getting married. She was referred to us at the age of 50 because of increasing difficulty in walking caused by pain in the right ankle. There were no new neurological symptoms and no symptoms of autonomic dysfunction. She was being treated with a non-steroidal anti-inflamatory drug and was on hormone replacement therapy. She had not received any psychotropic medication. Both her parents were caucasian and had died in their 80s. They had had no neurological illnesses, and there was no consanguinity. The patient has two siblings and three children of her own, all of whom are well with no neurological disorder.

Examination showed a severe dystonia which made her speech very difficult to comprehend. Psychometric testing, however, showed her performance to be in the average range, with a verbal IQ of 105. There was no non-verbal part of the WAIS-R was not performed because of limited manual dexterity, but good average scores were achieved on three years of non-verbal reasoning. There was a left exotropia, but eye movements were otherwise normal. There was pronounced lingual dystonia and orofacial dyskinesia. Her right leg was hypoplastic and she used callipers and two sticks to walk. There
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