Short report

Progressive medullary failure associated with neurofibrillary degeneration

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SUMMARY A clinicopathological report is presented of a British male, aged 59 years, who died after an illness of 10 years, manifested by progressive respiratory failure, ptosis, and dysphagia. At no time was there evidence of ophthalmoplegia, Parkinsonism or dementia. At necropsy the main finding was of neurofibrillary tangles in the neurons of the pontine and medullary reticular formation, with particularly severe involvement of the nucleus ambiguus, dorsal motor nucleus of the vagus and nucleus tractus solitarius. Morphologically, by light and electron microscopy and immunostaining, the tangles were similar to those of other neurofibrillary degenerative diseases. Although similar in some respects to progressive supranuclear palsy and amyotrophic lateral sclerosis of the Guam type, the combination of clinical and neuropathological features suggest that this is a distinct disease entity.

Neurofibrillary degeneration has been described in a variety of neurodegenerative conditions of unknown cause, presumably the result of diverse aetiologies.[1] What distinguishes these conditions from each other is their differing clinical presentations and topographic distribution of pathology. Although there are some histological differences, their appearances are remarkably uniform at the cellular level. This clinicopathological report is of a case with a rare variant in the general category of slowly progressive neurodegenerative disorders marked by neurofibrillary pathology which in this instance is focused particularly on neurons of the medulla.

Case report

The patient was well until the age of 49 years. Over an 18 month period he experienced difficulty in swallowing, choking episodes, and shortness of breath. He first came to medical attention in 1978 after collapsing at home, probably due to respiratory arrest. Neurological examination at this time was not significantly abnormal. Over the next year he developed bilateral ptosis without diplopia. In 1983 he was

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noted to be mildly diabetic. An episode of lobar pneumonia necessitated intubation for ventilatory support. Because of progressive dysphagia, dyspnoea, daytime somnolence, and generalised weakness he was admitted to the regional hospital for further evaluation, and then referred to the National Hospital, Queen Square, in 1986.

The patient's mental state was normal. He had bilateral ptosis and horizontal nystagmus but full extraocular movements. Palatal movement was poor and the gag reflex was absent; examination of the cranial nerves otherwise showed no abnormality. There was generalised wasting and weakness of the limbs, most notably in the triceps, but tone was normal, and there was no tremor. The jaw jerk was brisk, and the tendon reflexes in the limbs slightly increased, but the plantar responses were flexor. Gait and sensory examination were normal. He was noted to have sleep apnoea. During this admission he was found to be hyponatraemic due to inappropriate secretion of antidiuretic hormone; this possibly followed gram-negative septicaemia. Respiratory arrest while in hospital was followed by a tonic-clonic seizure.

Laboratory investigations included serum sodium 124 mmol/l, and blood sugar 17·7 mmol/l, but otherwise normal haematology and chemistry, negative screen for autoantibodies, normal blood gases and pH. An ECG showed evidence of old myocardial infarction. CT and MRI scans demonstrated generalised cerebral atrophy and periventricular lucencies, but no brainstem lesions. Nerve conduction studies and electromyography showed evidence of denervation in the arms. A muscle biopsy was performed which showed grouped fibre atrophy indicative of partial denervation. Because of apnoea and difficulty in maintaining nutrition in the face of bulbar dysfunction, a tracheostomy

and gastrostomy were performed and the patient discharged home.

Over the next 9 months he was able to manage at home. There was no evidence of declining cognitive function or of movement disorder. He died at home of respiratory failure, after an illness of 10 years duration.

Neuropathology

The necropsy (Dr P E Richardson) revealed bilateral bronchopneumonia; there were no other abnormalities. The brain weighed 1415 g (fixed) and appeared normal externally. The meninges were thin and transparent; the cranial nerves and basal vessels were normal. The size and configuration of the pons, medulla, and spinal cord were normal. On coronal slicing there was minimal dilatation of the lateral ventricles, but no other evidence of atrophy. The cortical ribbon, subcortical white matter, and deep grey nuclei were normal. The midbrain was of normal size and the substantia nigra was normally pigmented.

Blocks were taken from representative regions of the cerebral hemispheres, cerebellum, brainstem, spinal cord, peripheral nerves, and skeletal muscle. Paraffin sections were stained by a variety of routine neurohistological methods including silver impregnation of axons by the method of Glees. Where appropriate, selected blocks were also processed for immunostaining with antisera against glial fibrillary acidic protein (GFAP) and phosphorylated neurofilaments (RT97),[2] and ultrathin sections made from epon embedded tissue for electron microscopy.

The most striking abnormality was apparent in the midbrain, pons and medulla, where there was selective loss of neurons, gliosis, and neurofibrillary tangles (NFT) in some of the remaining neurons (fig 1, a). Some NFT resembled densely wrapped balls of yarn filling the perikaryon of affected neurons—the so called "globose tangles".[3] In other cases they had a more filiform appearance, extending into neuronal processes—the "flame shaped" tangles. This

distinction appeared mostly to reflect the shape of the neuron involved. Some of the NFTs were argyrophilic, but others did not stain with silver and could be seen as a negative image of transparent strands in the yellow-brown cytoplasm. The NFT were uniformly birefringent in both haematoxylin-eosin and Congo red preparations. In immunocytochemical preparations using the anti-phosphorylated neurofilament antibody (RT97) the NFT were always reactive (fig 1, b). The strongest staining was in the elongated or flame-like tangles, whereas the staining of the globose tangles was more delicate. As others have reported, the neurofilaments that make up the NFT are very resistant to postmortem autolysis,[4] and despite considerable postmortem artefact in this case, NFT could regularly be identified ultrastructurally as being composed of neurofilaments with a paired helical configuration (fig 1, c). They were disposed as relatively straight isolated pairs of filaments, as well as in bundles or aggregates.

In the mesencephalon, pathological alterations were most apparent in the dorsal raphe nucleus, where many neurons containing NFT were found along and adjacent to the midline, ventral to the oculomotor nuclei. An occasional NFT could also be found in neurons in the lateral parts of the substantia nigra, and scattered as single isolated cells in the tegmentum. Some of the NFT in the substantia nigra occurred in otherwise normal appearing pigmented neurons. No pigment laden macrophages or Lewy bodies were present in the substantia nigra and there was a normal complement of pigmented neurons. The red nucleus, pretectal area, superior colliculus, and oculomotor nuclei were not significantly affected. In the pons NFT were numerous in the midline raphe nucleus (centralis superior) and in the locus coeruleus, and affected cells were scattered in the tegmentum. In the locus coeruleus, NFT of the globose type were found in otherwise normal pigmented neurons. The population of pigmented neurons was not obviously depleted. The neurons of the basis pontis were unaffected. The cerebellum showed acute hypoxic pathology and some folia showed loss of
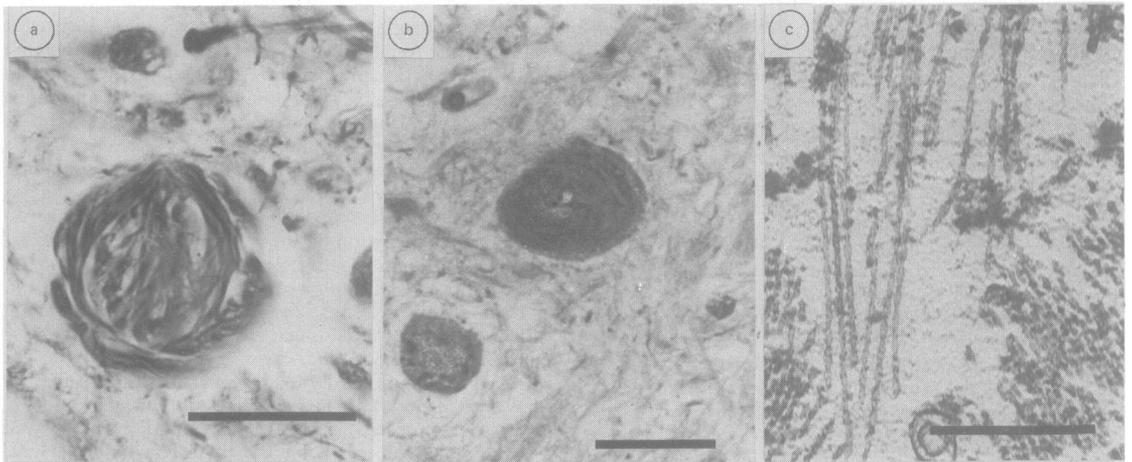
Fig 1 *Neurofibrillary tangles in neurons of the dorsal nucleus of the vagus, shown by silver impregnation (Glees' method) in (a) and by immunoperoxidase staining with antibody to neurofilament protein (b). The paired helical configuration of the filaments is shown in the electron micrograph of neurofibrillary tangles in a medullary neuron (c).*
(Scale bar = 20 μm for (a) and (b); 0·5 μm for (c).)

Purkinje cells and empty baskets. However, the overall architecture was normal and there was no neuronal loss, gliosis, or NFT in the deep nuclei. In the medulla the nuclei most severely affected were the dorsal motor nucleus of the vagus, the nucleus of the tractus solitarius, and the nucleus ambiguus. In each of these the number of neurons was diminished, and the nucleus appeared markedly gliotic in phosphotungstic acid—haematoxylin and GFAP preparations. The nucleus ambiguus was difficult to locate with confidence since its boundaries with the tegmentum were not well defined, and with marked neuronal cell loss delineation had become more difficult. Nevertheless, a few cells with NFT were found ventrolateral in the tegmentum in a location which corresponds to the nucleus ambiguus. A moderate number of NFT-containing neurons were scattered throughout the medullary tegmentum and raphe. The hypoglossal nucleus and inferior olive were unaffected.

The spinal cord was examined at cervical, thoracic, lumbar and sacral levels in transverse sections. The motor neuron pool appeared somewhat depleted, especially in the cervical region, and particularly affecting the medial cell column (by comparison with age matched control cases). At no level was there a complete absence or more than moderate depletion of motor neurons. The dorsal horns and intermediolateral columns were normal. The myelinated tracts, and in particular the corticospinal tracts were well myelinated. No NFT were found in any spinal neurons. The dorsal root ganglia, sympathetic ganglia, and peripheral nerves sampled at many sites were normal.

Sections of skeletal muscle from several locations showed denervation changes consistent with the slight degree of neuronal loss in the anterior horns. Small angulated fibres, and a slightly increased number of fibres with internal nuclei were found in muscles of the upper and lower extremities as well as in psoas and diaphragm. Muscles innervated by cranial nerves were not sampled.

In contrast to the brainstem and spinal motor apparatus, the cerebrum was less affected. In the hippocampus there were many argyrophilic and immunoreactive flame shaped NFT in many of the pyramidal neurons, especially in Sommer's sector. Granulo-vacuolar degeneration also affected some of these neurons, and senile plaques with amyloid cores (Alzheimer type) occurred in moderate numbers in the surrounding neuropil. Occasional tangles were found in the dentate fascia.

There were senile plaques with amyloid cores in the cingulate, frontal and temporal cortex. In these same regions there were no neuronal NFT. There was little or no detectable neuronal loss and the laminar pattern was unaffected. The cortex outside these regions was normal; in particular, the giant pyramidal cells of Betz in the motor cortex were normal in size, number and distribution.

A few cells with NFT were present in the nucleus basalis of Meynert, the medial hypothalamus and midline thalamus. The subthalamic nucleus and globus pallidus were unaffected; the number of neurons appeared normal and there were no NFTs or gliosis.

Discussion

The clinical and pathological findings in this case are closely complementary. The most marked pathology,

confined to the brainstem, involved the dorsal motor nucleus of the vagus, the nucleus of the solitary tract, and the nucleus ambiguus, with a lesser and more diffuse involvement of the pontine and medullary tegmentum (fig 2). These are the nuclei known to be involved in bulbar function and the generation and maintenance of respiratory rhythm.[5] Vascular and neoplastic lesions in these regions produce deficits in the same modalities as our patient's dysfunctions.[6] Likewise the degree of weakness that was noted on clinical examination, as well as the electrophysiological findings, would fit with the mild loss of anterior horn cells. Important negative findings were that this patient had no impairment of extraocular movement, extrapyramidal symptoms, or dementia, even at the end of a protracted course. In keeping with this, the pretectal area, superior colliculus, nigrostriatal system, and the cerebral hemispheres were for the most part not affected.

Whether this complex of clinical and pathological features fits any of the described neurodegenerative entities is problematic. It is not typical of any known disease and the question is whether it is an unusual variant of one of them. There are two general
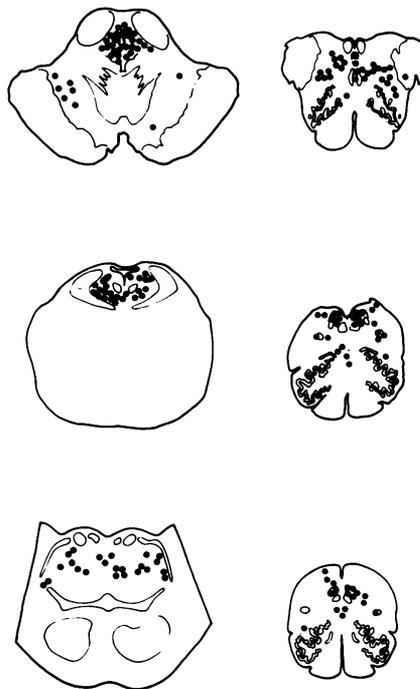
Fig 2 *Diagrammatic representation of the distribution of neurofibrillary tangles (solid dots) at various levels of midbrain pons and medulla. The distribution of NFT mirrors the areas severely affected by neuronal loss.*

categories of neuro-degenerative disease that appear to be related to the present case. On the grounds of cellular pathology a similarity to progressive supranuclear palsy (PSP) is suggested.[7-9] PSP is characterised by cell loss and the appearance of NFT selectively in brainstem nuclei. Cytologically these NFT are similar to those seen in the present case. The topographic distribution, in contrast, is quite different. In PSP there is significant involvement of the globus pallidus, subthalamic nucleus, pretectal area, superior colliculus, and cerebellar dentate nucleus, all of which were unaffected in the present case. In keeping with the distribution of pathology, the major clinical features in PSP are abnormalities of eye movement and extrapyramidal manifestations, none of which were features here. Even in the small group of cases which have been reported as PSP on pathological grounds despite the absence of ophthalmoplegia, the predominant clinical picture was of dementia and/or Parkinsonism.[10-12] Respiratory failure has not been reported as a feature of PSP, while it was the main clinical feature of the present case.

From a clinical standpoint the present case has some resemblance to bulbar amyotrophic lateral sclerosis (ALS) but the course was protracted and there were additional features of brainstem dysfunction, including ptosis and nystagmus. Also, on pathological criteria the present case does not appear to be the common or sporadic form of ALS. Neurofibrillary pathology has been looked for extensively in this condition, and does not occur.[13] Alternatively, the Guamanian form of ALS has largely occurred in the Chamorro population of Guam and certain other Pacific ethnic groups, and has a higher familial incidence and longer survival than sporadic ALS.[14] Clinically, these patients have bulbar dysfunction and generalised amyotrophy, but some also develop varying Degrees of dementia and extrapyramidal symptoms.[15] Pathologically, the disease is characterised by Alzheimer-like changes in the telencephalon, pallor of the substantia nigra, and the formation of NFT in neurons of the nigra, periaqueductal grey, reticular formation and brainstem motor nuclei.[16-20] The spinal cord always shows loss of anterior horn cells, pallor of the corticospinal tracts, and in some instances NFT in the remaining anterior horn cells.

The strongest reason for considering the present case in the light of Guamanian ALS is the similarity of some of the pathological features. The distribution of NFT and cell loss falls within the range of topographic distributions in the published reports. Whether the lesions are quantitatively similar is more difficult to gauge. This similarity does not hold in two areas, the substantia nigra and the corticospinal tracts, both of which are much more severely affected in the Guamanian disease. Moreover, the Guamanian disease occurs almost exclusively in specific Pacific ethnic groups. The very rare reported occurrences outside these groups has been explained on a supposed toxic aetiology.[22-23] In either event an inherited or environmental basis is implied. The occurrence of an isolated case in an Englishman, without any known history of foreign travel, environmental exposure, or unusual dietary practices, would be unlikely. The present case may be closest to the single case incidentally reported by Hirano of a man in New York City with an ALS-like syndrome and a pathological picture indistinguishable from the Guamanian disease.[13] In that case there was the suggestion of dementing and Parkinsonian features, but clinical details were scant.

Although we do not consider that a definite conclusion is possible, this case may be regarded as having some resemblances to the disease that has come to be called "Guamanian ALS" despite certain clinical and pathological differences and despite the obvious geographical difference. Alternatively, it may represent a unique variant of focal or systematised neurodegenerative disease affecting predominantly the medulla.

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