Selective and asymmetric vulnerability of corticospinal and spinocerebellar tracts in motor neuron disease

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SUMMARY The spinal cords of 10 cases of motor neuron disease were compared with those of six age-matched controls using myelin and silver impregnation methods, and the Marchi reaction for myelin degradation products. These studies revealed striking asymmetry in involvement of the lateral and anterior corticospinal tracts, without concordance in the pattern of involvement of these crossed and uncrossed corticospinal pathways. In addition there was prominent involvement of the posterior and anterior spinocerebellar tracts, but less marked abnormality was seen in the reticulospinal pathways. These findings highlight the asymmetrical involvement of the upper and lower motor neuron components of the motor system that is a characteristic feature of the disease, and demonstrate that involvement of the spinocerebellar system is a frequent finding.

Motor neuron disease is a progressive and fatal disorder of the motor system, characterised by clinical and pathological features of coexistent upper and lower motor neuron degeneration.¹⁻⁴ Involvement of the motor system may be strikingly asymmetrical.⁵ Sensory involvement is not evident to ordinary clinical examination but, in some cases, paraesthesiae have been noted,^{6,7} and subclinical abnormalities have been found in teased fibre preparations of sensory peripheral nerves.⁸ In the spinal cord the major abnormalities comprise loss of anterior horn cells and degeneration of the crossed and uncrossed corticospinal tracts.⁹⁻¹¹ Degeneration of the spinocerebellar tracts has been described in familial cases¹² but is thought to be infrequent in the more common sporadic form of the disease.^{2,3,13} However, no systematic pathological study has been made of non-corticospinal pathways in the spinal cord in sporadic motor neuron disease.

In a previous study we showed that loss of anterior horn cells in the disease is both asymmetrical and focal within individual spinal segments,⁵ and recent electrophysiological investigations have shown that there is asymmetrical slowing of motor conduction in the spinal cord.¹⁴ In this report we describe the pattern of degeneration in the descending and ascending

tracts in the spinal cord, especially in the crossed and uncrossed corticospinal tracts and in the spinocerebellar pathways. These observations show that the pattern of corticospinal tract involvement is variable and often asymmetrical, and that the pathological changes in the spinal cord usually extend beyond the upper and lower motor neurons to involve spinocerebellar pathways.

Materials and methods

The spinal cords of 10 patients with motor neuron disease, and of six age-matched control patients who had died without neurological disease, were studied. These cords were obtained from the necropsy records of the Institute of Pathology, The London Hospital, and from the Department of Neuropathology at the Institute of Psychiatry, London. In each of the 10 cases of motor neuron disease the diagnosis had been established during life by the typical clinical features,⁴ the progressive course, and by the exclusion of other causes following appropriate investigation in a neurological unit.⁴ None of these patients had been re-examined by a neurologist in the months prior to death. In each case, however, the diagnosis was confirmed by post mortem examination.

All the cords were fixed by immersion in 10% formal-saline. Blocks were taken from the C7, T6 and L3 segmental levels, processed in routine fashion through serial alcohols and chloroform, and embedded in paraffin wax. Serial transverse sections, 9 µm thick, were cut and consecutive sections were stained with haematoxylin and eosin, Luxol fast blue or cresyl fast violet, by Weil's method for myelin and with an immunoperoxidase technique for myelin basic protein. In addition, in each cord some sections were impregnated with

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Fig 1 *Weil's method for myelin. There is pallor of all the anterior spinal pathways, with sparing of the posterior columns. There is marked pallor of the crossed and uncrossed corticospinal tracts; the pallor of the lateral corticospinal tracts extends toward the surface of the cord suggesting involvement of the posterior spinocerebellar tracts.*

silver, using the methods of Palmgren, and of Marsland, Glees and Erikson. Additional blocks of the formol-saline fixed tissue were prepared using the Swank and Davenport modification of the Marchi technique for myelin degradation products, and subsequently processed into paraffin wax and sectioned in the transverse plane. The sections produced by these different methods were examined by two of us (MS and CLS) in a formal analysis in which the sections, both from the cords of the 10 patients with motor neuron disease and from the six control patients without neurological disease, were coded by GV and presented "blind" for assessment of the distribution and type of abnormality. Later, the sections of the cords were studied in more detail in the usual open fashion.

Results

In the cords from the 10 patients with motor neuron disease there was a marked loss of anterior horn cells that was especially marked in the sections taken from the C7 segments. There was no constant pattern of abnormality in the fibre tracts of the spinal cords of these cases, but abnormalities were particularly evident in the corticospinal and spinocerebellar pathways. There was generalised pallor of anterior spinal pathways in all the cords studied, often to a striking degree (fig 1), but posterior columns were normal, apart from an impression of slight pallor in the medial portions of the gracile columns in some cases. Selective damage to fibre tracts was recognised by loss of fibres in the silver impregnations, and by pallor in the sections stained by Weil's method and in the immunochemical preparations demonstrating myelin basic protein. However, the Marchi technique was the most informative since it demonstrated reaction product in the abnormal fibre tracts, indicative of degenerating

Fig 2 *Marchi method. There is striking degeneration in the lateral corticospinal tracts, but no involvement of the anterior corticospinal tracts.*

myelin in the abnormal fibres.^{15 16}

In nine of the 10 cases the crossed, lateral corticospinal tracts showed more abnormality in the Marchi preparations than the smaller, uncrossed anterior corticospinal tracts. In one case the uncrossed tracts showed no abnormality (fig 2). The ipsilateral and contralateral lateral and anterior corticospinal tracts were not necessarily affected to a similar extent, indicating that there was no constant relation between the extent of abnormality in these homologous components of the descending pyramidal motor system in the cord. Thus, in two cases the crossed and uncrossed corticospinal fibres were more affected on one side of the cord and, in four there was relatively selective involvement of the lateral tract on one side and of the anterior tract on the other. Unilateral involvement of the anterior or lateral corticospinal tracts was also noted in the Marchi preparations of two cases (fig 3). In these cords asymmetrical fibre loss was noted in the four corticospinal pathways in the silver preparations. In one case the corticospinal tracts appeared normal, although there

Fig 3 *Marchi method. Reaction product is present in one lateral corticospinal tract and in the contralateral anterior spinocerebellar tract.*

Fig 4 *Marchi method. Reaction product in one spinocerebellar tract. Myelin and silver preparations in this case showed loss of fibres in all four corticospinal tracts.*

was conspicuous loss of anterior horn cells, and one spinocerebellar tract showed Marchi positivity (fig 4).

The Marchi preparations also revealed bilateral, often asymmetrical, abnormalities in the posterior spinocerebellar tracts and, to a lesser extent, in the anterior spinocerebellar tracts (fig 4). It was sufficiently dense in some cords to obscure the anatomical separation of the lateral corticospinal and posterior spinocerebellar tracts (fig 5). In one cord there was involvement of only one of the posterior spinocerebellar tracts. In the cervical sections of one cord there was a slight accumulation of Marchi-positive material in the reticulospinal tracts and in the medial parts of the gracile columns. Although no attempt was made to count the remaining neurons in these cords there was a subjective impression of loss of neurons in the nuclei of Clarke's column.

The sections of the cords of the six control cases, prepared by the same methods, were all normal. No artefactual deposits of Marchi-positive material were seen in these sections.

Discussion

No constant pattern of involvement of the homolateral or contralateral corticospinal pathways in the cord was observed in these studies. Indeed, in the Marchi preparations there was a striking lack of correlation between the changes noted in the crossed and uncrossed corticospinal tracts. In some cases there was degeneration in the ipsilateral crossed and contralateral uncrossed corticospinal tracts as would be expected if there was predominantly unilateral involvement of the corticospinal system at more rostral

level of the nervous system. In others there was independent involvement of the homolateral and contralateral tracts. In some cases, in addition to the presence of myelin degradation products in the corticospinal tracts, there was Marchi positive material in the posterior spinocerebellar tracts and, less commonly, in the reticulospinal tracts and in the posterior columns. Involvement of the spinocerebellar tracts thus appears to be a more constant feature of the disease than has hitherto been considered.^{11 13} Involvement of the spinocerebellar tracts in motor neuron disease is asymmetrical, a distribution of abnormality different from the typically symmetrical pathological changes found in these pathways in the familial and metabolic spinocerebellar degenerations.¹⁷

Smith^{15 16} used the Marchi technique to study the distribution of degeneration of the central motor pathways at necropsy in seven cases of motor neuron disease. She noted that there was evidence of abun-

Fig 5 *Marchi method. Reaction product is present to a similar extent in the lateral corticospinal tract and of the anterior and posterior spinocerebellar tracts, so that there is no clear demarcation between those two pathways in this cord.*

dant degeneration at all levels of the corticospinal system and, in some cases in the thalamus, corpus callosum and superior colliculus. Pallor of myelin staining was observed, as a general phenomenon, in the anterior spinal pathways, but not in the posterior columns. This pallor in the anterior parts of the spinal white matter was also noted by Brownell *et al.*¹¹

Brownell *et al.*¹¹ noted a number of features at variance with the classical accounts of the pathology of the disease.^{9 10} Thus, in eight of their 36 typical cases of motor neuron disease there was no abnormality of the corticospinal tracts. Lawyer and Netsky¹⁰ also observed sparing of the corticospinal pathways in two cases. Brownell *et al.*¹¹ noted that the corticospinal tracts were often affected asymmetrically, but they did not find specific abnormalities in the spinocerebellar tracts, although they commented on pallor of the myelin in these regions of the cord. They did not use the Marchi method in their investigation. Since there is involvement of the neurons of Clarke's column in the disease,^{18 19} degeneration of the spinocerebellar tracts is probably a regular part of the disease process, rather than an occasional or complicating feature.

The fibres of the posterior spinocerebellar tracts, which were most affected in our cases, arise in Clarke's dorsal nucleus and ascend lateral to the lateral corticospinal tract to synapse in the restiform body and in the vermis and pyramis of the cerebellum.²⁰ Fibres in these tracts convey impulses derived from muscle spindles and other receptors in muscles and joints. Histological studies of muscle spindles using the silver chloride block impregnation method to demonstrate the innervation²¹ have shown that there is degeneration of both the alpha and gamma motor innervations of the intrafusal muscle fibres in motor neuron disease. However, the primary and secondary sensory innervations of the muscle spindles appear histologically normal, even at necropsy.²¹ The functional significance of degeneration of the spinocerebellar tracts is thus not readily apparent.

Asymmetry is a fundamental feature of motor neuron disease that is evident clinically,^{5 22} electrophysiologically,^{23 24} and pathologically,⁵ both in the infranuclear and supranuclear portions of the motor system. There is no evidence that this relates to the amount of use of individual pathways or subsets of the motor system. Current theories of the pathogenesis of the disease do not offer any appropriate explanation for this asymmetry,^{2 3 5} or for the other specific features, including the loss of both alpha and gamma motoneurons,^{5 21} and the relative resistance of certain other motoneuronal groups to the disease process.^{5 24 25}

The rate of degeneration of the upper and lower motor neurons in the disease, and the interrelation between degeneration in these two systems, are

important concepts in understanding the disease, but little is known about this. The Marchi technique detects myelin degradation products 10 to 20 days after a lesion, and these degradation products are gradually removed during the subsequent year.¹⁵ Thus the presence of well-marked reactivity in the Marchi preparations of cords from patients with motor neuron disease implies that degeneration in the affected pathways has occurred as a continuous process, at least up to several months before death. This interpretation is consistent with the results of clinical and electrophysiological studies of the pattern of progression in the disease.^{24 25}

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