5 The Pathology of Motor Neuron Disease

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Introduction

In the descriptions of progressive muscular atrophy by Aran (1850) and Duchenne (1853) and of progressive bulbar palsy by Duchenne (1860) involvement of the muscular and not the nervous system was implicated. This issue was hotly debated (Cruveilhier 1853; Luys 1860), and an abnormality of the nervous system came to be regarded as the prime pathogenetic mechanism. Consistent central nervous system involvement in these disorders was described by Charcot and Joffrey (1869) and Charcot (1870). The term amyotrophic lateral sclerosis was introduced by Charcot (1874) following his demonstration of pyramidal tract lesions in cases of progressive muscular atrophy. Dejerine (1883) championed the now generally accepted view that progressive muscular atrophy, progressive bulbar palsy and amyotrophic lateral sclerosis are clinical variants of the same disorder: motor neuron disease (MND).

The cardinal pathological features of MND are loss of anterior horn cells, and of motor cells in the lower cranial nerve nuclei, and degeneration of the crossed and uncrossed corticospinal tracts. The classical descriptions of the pathology, based on autopsied cases, represent the end-stage of the disease (Holmes 1909; Bertrand and Van Bogaert 1925; Lawyer and Netsky 1953; Brownell et al. 1970; Castaigne et al. 1972). In addition to involvement of the motor system, there is loss of neurons in Clarke's column (Holmes 1909; Averback and Crocker 1982) and this is associated with degeneration of the spinocerebellar tracts (Averback and Crocker 1982; Williams et al. 1990). Although myelin is generally pale in the anterior and lateral parts of the cord, the posterior column myelin is usually normal, apart from a minor degree of pallor in the gracile columns. However, in familial cases, pallor of the posterior columns may be more prominent (Iwata and Hirano 1979). Several variant forms of MND are well recognised including an association with dementia and with parkinsonism (Feller et al. 1966; Boudouresques et al. 1967; Farmer and Allen 1969; Mitsuyama and Takamatsu 1971; Reed and Brody 1975; Horton et al. 1976; Hudson 1981; Mitsuyama 1984).

In most major series the presence of familial forms of MND and of atypical cases, either in clinical picture or neuropathological findings, raises the question of the relationship of classical MND to other neuronal degenerations (Lawyer and Netsky 1953; Brownell et al. 1970). Recent studies of the genetics of spinal muscular atrophies and MND, together with advances in the pathological study of MND and other disorders using immunohistochemical techniques, may help to clarify some of these questions.
General Autopsy and Neuropathological Findings

At autopsy the striking feature is often of profound muscular atrophy, this feature being the basis of Aran's and Duchenne's belief in a myopathic process being responsible for the condition (Aran 1850; Duchenne 1860). In earlier series the muscular atrophy was compounded by cachexia, particularly in cases of bulbar palsy, but this is less common with the advent of assisted feeding by nasogastric tube or by gastrostomy where appropriate. Death often results from respiratory failure, complicated in the majority of cases by the presence of bronchopneumonia (Charcot and Joffroy 1869; Puscariu and Lambior 1906; Dagnelie and Cambier 1933; Lawyer and Netsky 1953; Carpenter 1968; Brownell et al. 1970; Hughes 1982; Averback and Crocker 1982). Aspiration of food or gastric contents into the respiratory tract is perceived as a clinical problem in the care of patients with MND, and whilst aspiration of small quantities of food may contribute to pulmonary infection or infarction (Lawyer and Netsky 1953), this is considered to result from recumbency (Hughes 1982). In fact, aspiration of food or gastric contents does not appear to be a direct cause of death in any major autopsy series. In two of the most completely reported general autopsy series additional findings included cerebral haemorrhage, atherosclerosis, thyroid adenomata, aortic aneurysm, trichinosis, duodenal ulcer, carcinoma of the colon, carcinoma of the kidney and myelomatosis (Lawyer and Netsky 1953; Brownell et al. 1970). These findings are consistent with coincidental pathological findings in an autopsy series in this age group (Hughes 1982, Henson and Urich 1982).

There is a striking absence of bedsores in patients dying with MND, despite the profound degree of incapacity prior to death (Charcot 1874; Forrester 1976; Fukukawa and Tokoyura 1978). It has been suggested that bedsores develop in patients with neurological disease due to vasomotor paralysis related to sympathetic nervous system dysfunction and that sympathetic vasomotor activity is spared in MND (Forrester 1976; Fukukawa and Tokoyura 1978). Preservation of sympathetic vasomotor tone corresponds with preservation of sympathetic neurons in the lateral horn of the spinal cord (Iwata and Hirano 1979).

Changes in skin collagen structure and in collagen and mucopolysaccharide content have been reported in MND (Fullmer et al. 1960; Ono et al. 1986). Other "systemic" structural alterations in MND include the association of abnormal liver function tests with the presence in liver biopsy specimens of swollen mitochondria and intramitochondrial inclusion bodies with a high copper content (Masui et al. 1985; Nakano et al. 1987).

Macroscopic abnormalities of the nervous system are well reported in MND. Cruveihier (1853) noted thinning of the anterior roots in MND in the celebrated case of Prosper Laconte, studied by Duchenne (described by Dejerine, 1883). Charcot and Joffroy (1869) and Dejerine himself (1883) confirmed anterior root atrophy occurring in cases of MND with both a clinical picture of progressive muscular atrophy and of bulbar palsy. In both these studies the thinning of the anterior roots is noted to be more pronounced in the cervical cord than in the lumbar region. Most authors agree that posterior roots are unaffected (Holmes 1909). However, there is some disagreement as to the appearance of peripheral nerves, some suggesting that there is no gross alteration (Lawyer and Netsky 1953; Hughes 1982), others claiming to observe atrophy (Dejerine 1883; Bertrand and Van Bogaert 1925). It is