Alternative Approaches to the Pathology of Motor Neuron Disease

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The pathology of motor neuron disease (MND) is well recognised, but poses many problems of interpretation and understanding. There is, as yet, no insight into the pathobiological mechanisms that underlie the development of the specific neurodegenerative changes that must characterise the disease. In order to try to understand this problem a number of other approaches have been tried. These include:

1. A search for naturally occurring and experimental models of MND
2. Studies of the motor end plate including axonal sprouting
3. Studies of axonal transport in the peripheral nervous system in MND

These alternative approaches to understanding of the pathology of MND are reviewed in this chapter.

Animal Models in the Study of MND

Two basic groups of experimental approaches have been used in this study and development of animal models designed to mimic human motor neuron disease. The two groups comprise naturally occurring animal models and experimentally induced MND-like disorders. At this time however, there is no animal model of MND that is generally agreed to adequately mimic the range of clinical and pathological features of the disease seen in man.

Naturally Occurring Animal Models of MND

The most extensively studied naturally occurring putative animal models of MND occur in the Brittany spaniel and the wobbler mouse. An autosomal dominant form of spinal muscular atrophy – hereditary canine spinal muscular atrophy (HCSMA) may develop in the Brittany spaniel. This disorder resembles the progressive muscular atrophy form of MND (Cork et al. 1979). In this model the affected dogs
develop a rapidly progressive, predominantly proximal weakness if homozygous for the trait, whereas heterozygotes have milder or more chronic disease (Sack et al. 1984). The pathology of the canine disease is notable for the prominence of axonal spheroids in the anterior horn of the spinal cord (Cork et al. 1982), a feature also seen in human motor neuron disease (Carpenter 1968; Sasaki et al. 1988). In HCSMA there is thought to be a disturbance in the slow components of axonal transport (Griffin et al. 1982) and neurofilaments accumulate in neuronal perikarya. The model is useful in the study of genetic influence in human MND, and the presence of axonal swellings in anterior horns suggests some relationship to the pathology of human MND. It is well recognised, however, that in the commonest form of human MND, i.e. sporadic MND, there is no simple relationship between genetic history and disease (Mulder et al. 1986; Kurtzke and Beebe 1980). Similarly, the pathological findings in motor neuron disease, whilst including axonal swellings (Carpenter 1968), also include other features such as Bunina bodies (Bunina 1962) and Hirano bodies (Hirano 1965), not found in HCSMA. In addition, there is no loss of motor neurons in HCSMA. Hirano bodies associated with degeneration of cortical and hippocampal neurons may be found in a natural murine mutant, the brindled mouse, characterised by a deficiency in copper metabolism (Nagara et al. 1980). The clinical and pathological features of the neuronal degeneration in the brindled mouse are however, otherwise unlike those found in human MND. A spontaneous lower motor neuron disease that has been suggested as a possible model for the human disorder may also develop in rabbits and pigs and an hereditary amyotrophic disorder in pointer dogs has been described, although preliminary neuropathological studies failed to demonstrate neuropathological abnormalities of anterior horn cells (Yamaguchi et al. 1978).

The wobbler mouse is another naturally occurring disorder which has been used as a model of human MND (Duchen et al. 1968; Andrews et al. 1974). In this model affected mice develop weakness, atrophy and contractures chiefly affecting forelimb muscles, and the pathological changes are seen chiefly in the cervical cord (Duchen et al. 1968; Andrews 1975). The disorder is inherited as an autosomal recessive trait (Duchen et al. 1968). Affected mice are small for their age. The pathological features consist of vacuolation and degeneration of anterior horn cells, although only a small proportion of anterior horn cells are affected at any given clinical stage (Mitsumoto and Bradley, 1982). Occasionally dorsal root ganglion cells may also degenerate. There is abnormal protein synthesis in the anterior horn cells (Murakami et al. 1980) with accumulation of neurofilaments. Further, there is reduced regenerative capacity of these motor neurons after nerve crush (Mitsumoto 1985). Slow axonal transport has been found to be reduced in the distal nerve segments (Bird et al., 1971, Mitsumoto and Gambetti, 1983) representing data acquired from the mixed sensorimotor axons found in limb nerves. These abnormalities in the wobbler mouse have been ascribed to a primary neuronopathy according to the classification described by Spencer and Schaumberg (1981); that is, the degeneration starts in the neuronal perikaryon and then spreads to the proximal axon (Mitsumoto and Bradley 1982). This animal model is useful because the rapid timecourse of the degeneration permits many cycles to be studied, but it does not provide an accurate model of human motor neuron disease from the pathological or genetic point of view. However, it is useful in the study of neuronal degeneration and regeneration.

Another murine mutant, the “wasted” mouse, has been described by Shultz et al. (1982) and by Lutsep and Rodriguez (1989). The mutants, mice homozygous for the