AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS)
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Amyotrophic lateral sclerosis (ALS) is the most common form of Motor Neuron Disease, a group of disorders that involve progressive loss of movement as the motor neurons that control the voluntary muscles degenerate and are lost. Motor neurons control the muscles that cause body movement and are needed for walking, speaking, breathing and swallowing. The motor neurons that are present in the spinal cord and brain stem (lower motor neurons) directly control the muscles, whereas motor neurons that are present in the brain (upper motor neurons) control the lower motor neurons. ALS involves degeneration and loss of both the upper and lower motor neurons, whereas other types of Motor Neuron Disease involve loss of either upper or lower motor neurons. ALS is usually rapidly progressive and generally results in death within three to five years of diagnosis, in most cases from respiratory failure.

There are no distinctive diagnostic tests for ALS and diagnosis relies on criteria defined by the El Escorial criteria for diagnosis of MND (Ince *et al*., 1998). Clinical examination may be accompanied by electrophysiological testing and a positive diagnosis needs evidence of both upper and lower motor neurons symptoms in addition to evidence of progressive spread of the disease. Additionally, testing involves exclusion of symptoms associated with other diseases including sensory degeneration, autonomic dysfunction, visual disturbances, Parkinson's disease and Alzheimer type dementia. The first symptoms associated with ALS depend on the area of the nervous system that is initially affected by the disease. In the majority of cases the first symptom for spinal cord onset is asymmetrical weakness of one of the limbs or, with bulbar onset disease, slurring of speech (Leigh and Ray-Chaudhuri, 1994; Jackson and Bryan, 1998). Lower motor involvement causes weakness, muscular atrophy and fasciculation and signs of upper motor involvement include weakness, spasticity and hyperreflexia. Dysphagia and dysarthria may also be present (Leigh and Ray-Chaudhuri, 1994).

The incidence of ALS is reported as 1-2 per 100,000 (Roman, 1996) with approximately 90% cases being sporadic with no known cause. Only two proven risk factors have been identified, namely, age (incidence peaks around 60-70 years of age) and sex (men are more commonly affected with a ratio of 1.5 to 1). Other unproven risk factors include exposure to toxins, previous musco-skeletal injury, electric shock, exposure to heavy metals and heavy manual activities (Brooks, 1996). As with many

sporadic neurological disorders, the cause of disease is believed to involve components of both genetic disposition and environmental factors.

Although the majority of cases of ALS are sporadic, approximately 10% cases are inherited. The first gene responsible for causing ALS was identified in 1993 as copper-zinc superoxide dismutase gene (SOD1) (Rosen *et al*., 1993), which is responsible for causing approximately 20% of the inherited cases. This protein has a major role in antioxidant defences of cells, however the contribution of loss of antioxidant defence to the pathogenesis of the disease is widely disputed (Cluskey and Ramsden 2001; Shaw *et al*., 2001). A number of other genetic mutations have been identified including mutations in genes encoding the proteins TDP-43 and FUS, which play a role in the production of a range of other proteins in the cell. .Recently mutations have been identified in the DNA of ALS patients that does not code for any proteins so the role of these different mutations in the course of the disease is unclear. Furthermore, as these genes are expressed in most cells of the body, it is not understood why they cause the motor neurons to degenerate preferentially and not all cells. It is clear, however, that ALS is a multifactorial disease involving a number of different mechanisms of pathogenesis.

The major pathological finding in the central nervous system (CNS) of ALS is the selective loss of motor neurons in the anterior spinal cord, brain stem cranial nerves and motor cortex accompanied by corticospinal tract degeneration (Nihei *et al*., 1993), with relative sparing of the oculomotor and onufs nucleus (Milanos, 1998). However, there is mounting evidence that ALS is a multisystem disorder with the motor neurons being primarily affected, and loss of interneurons in motor cortical and spinal cord areas has been reported (Nihei *et al*., 1993; Stephens *et al*., 2006). Glial or non-neuronal cells are also likely to play a major role in the disease. Pathological analysis of motor neurons in the spinal cord reveals the presence of a number of intracellular inclusions including ubiquitinated bodies, the majority of which in sporadic disease contain TDP-43. Furthermore, there is a significant amount of axon degeneration and loss of the neuromuscular junctions, which may occur at earlier stages of the degeneration process. One of the current major questions that needs to answered in ALS is how the degeneration of the neurons and glia in different parts of the CNS affect each other and whether they are linked in a dying back (from the

muscle) or dying forward (from the motor cortex) fashion, or alternatively if the cell losses are independent of each other.

Despite recent advances in ALS research, there is an urgent need for effective treatments. Mouse models of ALS carrying the mSOD1 gene have been used to trial numerous potential drugs targeting the likely causative disease mechanisms and many of these have been successful. However, translating this success into human trials has proven difficult. Over 50 drugs have been trialled in humans since 1941 (Turner *et al*., 2001), all of which have been unsuccessful except for Riluzole, which has been shown to prolong survival by three months (Miller *et al*., 2003) and is the only current therapeutic intervention for the disease. Current strategies of therapeutic intervention are trying to overcome the complex multifactorial nature of ALS either by using combined therapies, which target multiple disease causing mechanisms (reviewed in Carri *et al*., 2006) or common pathways of neuron protection. It may also be important to target both neuronal and non-neuronal cells involved in disease progression. Critical to this search for a new and effective therapeutic for the treatment or cure of people with ALS is research designed to uncover and define the complex cellular mechanisms underlying the disease.

Brooks, B. R. (1996). Neurol Clin **14**(2): 399-420. Carri, M. T., G. Grignaschi, et al. (2006). Trends Pharmacol Sci **27**(5): 267-273. Cluskey, S. and D. B. Ramsden (2001). Mol Pathol **54**(6): 386-392. Ince, P. G., J. Lowe, et al. (1998). Neuropathol Appl Neurobiol **24**(2): 104-117. Jackson, C. E. and W. W. Bryan (1998). Semin Neurol **18**(1): 27-39. Leigh, P. N. and K. Ray-Chaudhuri (1994). J Neurol Neurosurg Psychiatry **57**(8): 886-896. Miller, R. G., J. D. Mitchell, et al. (2003). Amyotroph Lateral Scler Other Motor Neuron

Disord **4**(3): 191-206. Milonas, I. (1998). J Neurol **245 Suppl 2**: S1-3. Nihei, K., A. C. McKee, et al. (1993). Acta Neuropathol (Berl) **86**(1): 55-64. Roman, G. C. (1996). J Neurol Neurosurg Psychiatry **61**(2): 131-137. Rosen, D. R., T. Siddique, et al. (1993). Nature **362**(6415): 59-62. Shaw, C. E., A. al-Chalabi, et al. (2001). Curr Neurol Neurosci Rep **1**(1): 69-76. Stephens, B., R. J. Guiloff, et al. (2006). J Neurol Sci **244**(1-2): 41-58. Turner, M. R., M. J. Parton, et al. (2001). Semin Neurol **21**(2): 167-175.