4 Excitotoxicity, Genetics
and Neurodegeneration
in Amyotrophic Lateral Sclerosis

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4.1 Introduction

Amyotrophic lateral sclerosis (ALS) is one of the commonest human neurodegenerative disorders of adult life. The cell-death process in ALS is relatively selective for upper motor neurones, a proportion of which are represented by Betz cells (Fig. 1A) in the fifth layer of the motor cortex, and for lower motor neurones in the ventral horn of the spinal cord (Fig. 1B) and brainstem. The selective vulnerability of motor neurones in ALS is relative and, there is now increasing evidence from pathological (Ince et al. 1996; Iwanaga et al. 1997; Williams et al. 1995) and clinical (Chari et al. 1996; Kew et al. 1993; Subramaniam and Yiannikas 1990) studies that extra-motor system involvement commonly occurs, and that ALS is in fact a multisystem disorder. As a result of the neurodegenerative process, the individual afflicted by ALS develops progressive muscle weakness, wasting and spasticity and usually dies from respiratory failure within 3–5 years from the onset of symptoms. One of the interesting clinical features in ALS is that certain groups of motor neurones tend to be selectively spared from injury, including those brainstem nuclei innervating extraocular muscles responsible for eye movement and those in Onuf’s nucleus in the sacral spine cord innervating the muscles of the pelvic floor.

The degenerating motor neurones in ALS are characterised by the presence of ubiquitinated inclusion bodies (Leigh et al. 1988; Lowe et al. 1988). The inclusions may be hyaline, skein-like or Lewy body-like (Fig. 2A,B). In most circumstances, the major protein constituent of the fibrils comprising these inclusions is unknown although the most promising candidates are neurofilament epitopes. In some cases of familial ALS, hyaline conglomerate inclusions have been observed which demonstrate intense immunoreactivity for both phosphorylated and non-phosphorylated neurofilament epitopes (Shaw et al. 1997b; Fig. 2C).

The primary pathogenetic processes underlying ALS are likely to be multifactorial, and the precise molecular mechanisms underlying selective cell death in the disease are at present unknown. Current understanding of the neurodegenerative process in ALS suggests that two major mechanisms contribute to motor-neurone injury: (a) glutamatergic toxicity and (b) oxidative stress/free radical damage (Brown 1995; Coyle and Puttfarcken 1993; Ince et al. 1997).