Summary. Amyotrophic lateral sclerosis (ALS) is a degenerative disorder involving the upper and lower motor neuron sparing the extraocular and sphincter muscles. The course of the disease is relentlessly progressive with a mean survival time of 3 years. ALS occurs mainly sporadic (sALS) and is in about 10% of cases familial (fALS). Although the etiopathogenesis of ALS is still not known, the information on the pathomechanisms of motor neuron death has been mounting and a first drug has been shown to prolong survival. The important milestone in ALS research in the last decade was the finding that about 5 to 10% of the familial cases, i.e. 2% of all patients, carry mutations of the SOD1 gene.

1. INTRODUCTION

The first comprehensive description of the disease dates back to Charcot in 1873 who also coined the term amyotrophic lateral sclerosis (sclerose lateral amyotrophique) (10). His precise and systematic clinical observations still hold. He also described the involvement of the upper and lower motor neuron in post mortem studies. The term motor neuron disease frequently used in English speaking countries has been introduced by Gowers. Famous people dying from ALS were the US Baseball player Lou Gehrig, the movie actor David Niven and probably also Mao Tse Tung. Still alive, although on the respirator, is the astrophysicist Stephen Hawkings who has a very slow variant of the disease.

2. EPIDEMIOLOGY

ALS has a worldwide incidence of 1 to 2.5 cases per 100,000 and a prevalence of 3 to 8 per 100,000. These numbers appear to increase slightly over the last decades although it is unclear if improved diagnosis and prolonged survival or other variants such as environmental changes play the dominant role. Approximately 90% of the cases are sporadic (sALS) and the other 10% familial (fALS). The age of onset is 50 to 70 years peaking at 60 years although younger and older patients are common. The mean age of onset of fALS seems to be somewhat lower. There is a slight male preponderance (ratio male to female 1.6 to1) in sALS which is not seen in fALS. The mean survival time after disease onset is 3 years with considerably shorter and
longer (up to 20 years) time courses. The life expectancy has probably slightly improved because of modern treatment. An endemic form of the disease is found in the western Pacific (Guam, New Guinea, Japanese Kii Peninsula) clinically presenting as Parkinson-ALS-dementia complex with predominant involvement of the upper motor neuron. At the end of world war II there was a prevalence in Guam of about 100 per 100,000. It is still debated whether the incidence has declined after the occupation of the island and whether genetic or environmental factors are the major pathogenetic players.

3. CLASSIFICATION

Sporadic ALS can be clinically classified as follows:

- Classical ALS: clinical involvement of upper and lower motor neuron
- Progressive muscle atrophy (PMA): clinical involvement of the lower motor neuron only; upper motor neuron signs may occur with time
- Progressive bulbar palsy: begins mostly as pseudobulbar dysfunction and progresses usually to classical ALS
- Primary lateral sclerosis: pure upper motor neuron involvement over years; mild lower motor neuron signs may occur with time.

The recently revised "El Escorial Criteria" (14) define different levels of certainty of the diagnosis which may be of relevance for drug trials and other scientific purposes: The revised Criteria distinguish on clinical grounds:

- suspected ALS,
- possible ALS,
- probable ALS,
- definite ALS

and list as new categories

1. definite familial ALS laboratory supported:
   clinical condition which may fit with beginning motor neuron disease associated with molecular genetic testing positive for SOD 1 mutation

2. laboratory supported probable ALS:
   clinical condition fitting with possible ALS which reveals signs of active denervation in electromyographic studies in, at least, two limbs

Patients can usually be enrolled in controlled treatment studies only when they fulfil the criteria of probable ALS. The application of these new categories makes it possible to include patients earlier than in the past, i.e in clinical stages of the disease when treatment is more promising.