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AMYOTROPHIC LATERAL SCLEROSIS

Advances and Perspectives of Neuronanomedicine

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Preface

Amyotrophic lateral sclerosis (ALS) is one of the most devastating motor system neurodegenerative diseases, causing around 10,000 deaths each year. The neuropathology of ALS, which leads to muscle weakness, is mostly confined to motor neurons in the cerebral cortex, motor nuclei of the brainstem, and anterior horns of the spinal cord.

The major goal in treating ALS, currently, is to recognize the onset of the disease early in order to initiate appropriate therapy and delay functional and cognitive losses. Upon the discovery of mutated SOD1 in ALS, many hypotheses have been proposed on how mutant SOD1 could cause neurodegeneration, including aberrant redox chemistry, mitochondrial damage, excitotoxicity, microglial activation and inflammation, as well as SOD1 aggregation. Recently, the implication of biocompatible nanotechnologies set the stage for an evolutionary leap in diagnostic imaging and therapy. In this scope, the book provides a comprehensive overview of the hypotheses and the molecular mechanisms associated with the inflammatory processes in motor neuron disorders and presents the latest research studies on ALS, highlighting the recent findings using newly developed imaging modalities and the innovative approaches of highly sensitive molecular imaging. In addition, by using recently developed surface-enhanced nanoimaging microscopy, the book offers new perspectives on neuroimaging and insights into early diagnosis and promising therapeutic strategies.

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Chapter 1

Clinical Features of Amyotrophic Lateral Sclerosis

The aim of this chapter is to introduce some basic concepts about amyotrophic lateral sclerosis (ALS). We start by outlining the concepts of motor neuron diseases and the clinical features of ALS, and present some recent clinical case studies. This will act as a basis to understand the subsequent chapters.

1.1 What Is Amyotrophic Lateral Sclerosis?

Motor neuron disease, interchangeably known as amyotrophic lateral sclerosis (ALS), is a neurodegenerative disorder characterized by a progressive muscular paralysis reflecting degeneration of motor neurons in the primary motor cortex, brain stem, and spinal cord. The disease mainly affects patients between 50 and 70 years of age. ALS was originally described by the French physician Jean-Martin Charcot in the 1870s (Fig. 1.1). ALS is widely known as Lou Gehrig's disease, named after the famous baseball player Lou Gehrig, who died of ALS, and which confines star British physicist Stephen Hawking to the wheelchair (Fig. 1.2). ALS is universally fatal, with an average mortality of 5 years after onset.

Figure 1.1 Dr. Jean-Martin Charcot, who first described ALS in a publication in Paris (1869).

The phenotypic expression of ALS is highly heterogeneous and determined by four elements: (1) body region of onset, (2) relative mix of upper motor neuron (UMN) and lower motor neuron (LMN) involvement, (3) rate of progression, and (4) cognitive impairment. ALS causes progressive weakness, which may at first be mild and subtle, but becomes severe and eventually affects the breathing muscle machinery. This disease ultimately results in death. The onset of the disease is insidious, and symptoms may be disregarded by the patient for several weeks or months. The first physicians consulted are usually general practitioners, orthopedic surgeons, or rheumatologists and only rarely neurologists. Even in countries with well-developed healthcare systems, it takes a year on average before the diagnosis is made. Up to now the diagnosis of ALS is still a clinical one and electromyography (EMG) is the most important technical test to support the diagnosis. Laboratory tests

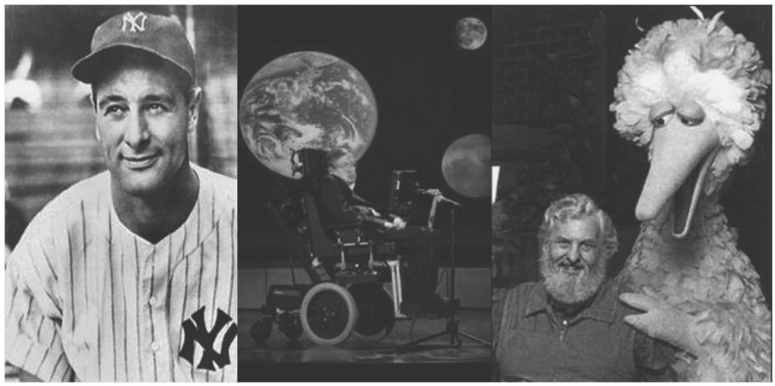

Figure 1.2 Notable people affected with ALS: (left) Lou Gehrig, Stephen Hawking, and (right) Jon Stone.

and imaging, including MRI, do not yield diagnostically positive results, but are necessary to exclude other potentially better treatable diseases.

1.2 ALS Signs and Symptoms

The first symptoms of ALS may be so subtle that they are overlooked: like muscle twitching, cramping, stiffness, weakness, involuntary jerking movements, tremors, inability to control the bowels or the bladder, or inability to move or open the eyes completely. As the weakness in the limb muscles progresses, muscle tissue is lost (atrophy), and the arms and legs begin to look thinner. Speech may become slurred, and later chewing and swallowing become difficult. Individuals with this disorder lose their strength, the ability to walk, and use of their hands and arms. Breathing becomes difficult because the muscles of the respiratory system weaken. Most people with ALS die from respiratory failure (Fig. 1.3).

There have been numerous debates on whether the upper or the lower motor neuron is first affected by the disease process. Upper motor neuron signs are preserved or exaggerated tendon reflexes in the presence of muscle atrophy and weakness. The muscle tone may be increased corresponding to spasticity more in the lower than

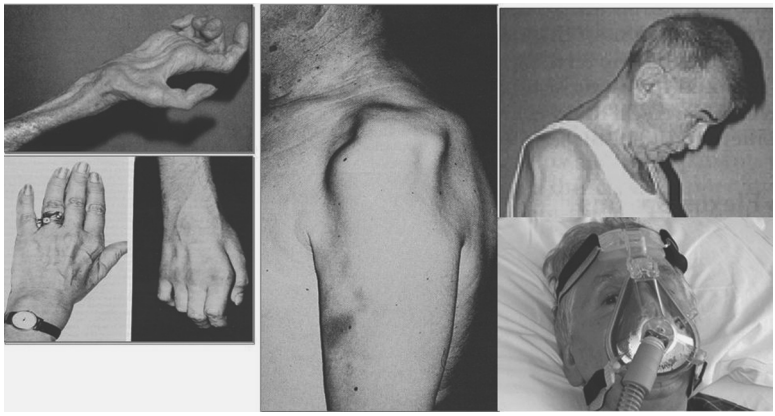

Figure 1.3 The hallmark of ALS is muscle denervation and wasting. Noninvasive ventilation of a patient with ALS. Photos courtesy of Robert Brown, MD, Harvard Medical School, Massachusetts General Hospital. V. McGuire et al., *Neurology* 1996;47: 571–573.

the upper extremities. In about 30% of the cases a Babinski sign may be observed. Signs of corticobulbar involvement are increased masseter reflexes, pathological laughing, crying, and yawning, which are also called pseudobulbar affect. The manifestation of upper and lower motor neuron features usually begins focally and progresses to involve contiguous regions of the body with decreasing severity. Approximately two-thirds of cases start in the limbs and one-third in the bulbar group of muscles; only a very small percentage of them begin with respiratory muscle involvement. Many patients, however, do not show signs of the upper motor neuron in early stages of the disease. Signs of the lower motor neuron are muscle atrophy, weakness, and fasciculations. In early stages of the disease, patients frequently speak of clumsiness and not so often of weakness. The onset of ALS is usually focal and asymmetrical: in somewhat more than 30% of the cases in the upper extremities, in about one-third in the lower extremities, and in about 25% in the bulbar region. A special phenotype is the so-called flail arm syndrome with onset of muscle weakness in the proximal upper extremities, while the legs may be spared for a long time. The flail leg syndrome with onset of the symptoms in the proximal lower extremities is observed less

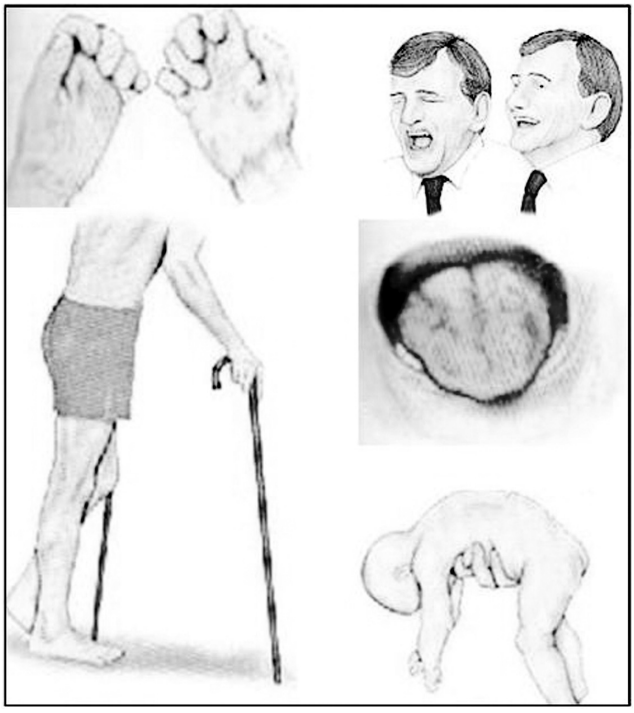

Figure 1.4 Lesions of both first and second motor neurons: paresis, muscular atrophy fasciculation, emotional lability, spastic paraparesis, tongue muscle atrophy, dysarthria, dysphagia.

frequently. These two phenotypes are characterized by an overall better prognosis, i.e., longer survival. Another special phenotype is progressive bulbar palsy. A distinction between pseudobulbar and bulbar involvement may be difficult, and the leading clinical signs are dysarthria and dysphonia in conjunction with dysphagia, atrophy, fasciculations of the tongue, and sialorrhea (Fig. 1.4). These patients frequently also show pseudobulbar affect. Survival is shorter than that of patients with disease onset in the extremities. Signs of an involvement of the autonomic nerve system, such as reduced perfusion of the extremities, decrease in the heart frequency variability, or changes detected in the electrocardiogram, can be observed. Sensory disturbances and pain are not typical for

ALS, although they have been described. Relevant sensory deficits raise doubts concerning the diagnosis. Respiratory insufficiency develops in the late stages of the disease and is a hallmark of the terminal phase. Loss of body weight frequently occurs early in the disease and may be caused by muscle wasting, dysphagia, and hypermetabolism. Very recently, an association between ALS and frontotemporal dementia has been increasingly discussed. While many patients show mild frontal signs, about 25% may manifest frontotemporal dementia. Depression may develop during the course of the disease and may, at least in some patients, become a relevant clinical aspect. It is not clear whether primary lateral sclerosis (PLS), a disease with selective upper motor neuron signs, is a variant of ALS or a distinct disease. A considerable portion of these patients, however, develop signs of the lower motor neuron over years. Progressive muscular atrophy (PMA) is characterized by pure lower motor neuron signs and otherwise resembles ALS. It has been suggested to regard PMA as a variant of ALS.

1.3 The Different Types of ALS

The different types of ALS have different causes. In approximately 5%–10% of patients, the disease is inherited; 20% of these individuals have a mutation of the SOD1 gene, approximately 2%–5% of the TARDBP (TDP-43) gene, and 2%–4% of the FUS/TLS gene. Most patients with ALS, however, have no obvious family history and have sporadic ALS. To date, the only specific marker of sporadic ALS is the presence of inclusions staining positively for ubiquitin and TDP-43 in degenerating motor neurons.

The genetic basis of ALS continues to be investigated (Fig. 1.5). Recently, mutations in the TTP-43 gene have been found to be a cause of some forms of ALS. Mutations in genes often encode proteins that function improperly. Mutations in TTP-43 form proteins that do not properly modify RNA (ribonucleic acid) in motor neurons. This is thought to contribute to the disease process. Identifying the genes and their abnormal protein products helps identify the targets for treatment.