Introduction and aims of the study
Motor neuron diseases include the most incapacitating and life-threatening illnesses but also rather benign disorders with only mild symptoms and slow progression. In motor neuron diseases, upper motor neurons and/or lower motor neurons can be affected. Upper motor neurons, which are located in the cerebral motor cortex, innervate lower motor neurons in the brainstem or in the anterior horns of the spinal cord, which through lengthy axons innervate multiple muscle fibers. The lower motor neuron, its axon with the surrounding myelin and the muscle fibers together form the motor unit.

This thesis focusses on lower motor neuron syndromes, in which only lower motor neurons are affected. It is important to determine within the group of lower motor neuron syndromes, whether primarily the lower motor neuron is affected (lower motor neuron disease, (LMND)), or alternatively the motor axon and its surrounding myelin (motor neuropathies). Furthermore, lower motor neuron syndromes have to be differentiated from other neuromuscular disorders affecting the neuromuscular junction or the muscle itself. In this respect, electromyography (EMG) and nerve conduction studies are important diagnostic aids.

In motor neuron diseases, motor neurons cannot regenerate if they perish during the course of the disease. Degeneration of lower motor neurons leads through axonal degeneration to denervation of muscle fibers. Denervated muscle fibers can be reinnervated by nearby axon branches from other still viable motor neurons through the mechanism of collateral sprouting, leading to enlargement of the motor unit (figure 1). With ongoing disease, the balance between denervation and reinnervation shifts towards denervation and enlarged motor units become at risk. The time course of denervation and loss of enlarged motor units determines the disease progression.

The classification of all motor neuron diseases is complicated by the different terminology in the USA, the United Kingdom and continental Europe. In this thesis we use the term motor neuron disease (MND) to describe all disease forms wherein motor neurons primarily degenerate (which only secondary may lead to damage to the axon and its surrounding myelin). The term amyotrophic lateral sclerosis (ALS) is used to refer to the “classical condition”, characterized by a combination of rapidly progressive upper motor neuron (UMN) signs and lower motor neuron (LMN) signs (see chapter 2). The term LMND is used for all diseases in which only lower motor neurons are affected. The term progressive (spinal) muscular atrophy (PMA or PSMA) is used to describe one of the several LMND forms (see chapter 3), and does not refer to all diseases of the lower motor neurons. The term motor neuropathies is used to denominate diseases in which primarily the axon and its surrounding myelin are affected.
**Lower motor neuron disease**

LMND is rare as the several forms of LMND account for less than approximately 10% of patients in several large series of MND. Also, LMND is not a well described clinical entity, and several clinical phenotypes have been described under various names. The question whether LMND is a distinct nosological entity separate from ALS, has been raised soon after its first clinical description by Aran in 1850.

Because a proportion of patients with LMND will eventually develop clinical signs of UMN degeneration or show pathological abnormalities of the corticospinal or corticobulbar tracts of the pyramidal cells at autopsy, it could be postulated that LMND and ALS are variants of a clinical spectrum. Compared with ALS, the disease course of LMND is thought to be slow. However,
only anecdotal cases or retrospective studies of small groups of patients with LMND have been published. More knowledge of the disease course in LMND is important to inform patients about the disease course and prognosis and also to consider treatment with riluzole, which is at date the only effective drug in ALS.

Genetic analyses may help to diagnose several LMND forms. For example, a deletion of the telomeric copy of the survival motor neuron (SMN) gene on chromosome 5q13 is sometimes found in some patients with adult-onset SMN gene-linked spinal muscular atrophy (SMA). In spinobulbar muscular atrophy or Kennedy disease, an expansion of CAG trinucleotide repeats in the androgen receptor gene has been recognized since 1991.121

**Motor neuropathies**

In motor neuropathies either the myelin sheath or the axon may be primarily affected. In multifocal motor neuropathy (MMN), the presence of persistent conduction block on electrophysiological examination supports an immune-mediated pathogenesis with primary involvement of the myelin sheath. The immunological attack is probably directed to the Schwann cells, which are responsible for the production and repair of myelin (figure 2). Consequent paranodal or segmental demyelination, that is caused by the inflammatory response, may give rise to reduction of nerve conduction velocity or motor conduction block. An alternative explanation could be that the axon, which has to be structurally intact to propagate nerve impulses, is the target of the immune response. The nodes of Ranvier which are formed by interruptions of the myelin sheath at regular distances, are necessary for the physiological process of saltatory conduction. The immunological process may damage the bare axon at the nodes of Ranvier and inflammation may lead to axonal degeneration and if severe, to axonal loss. The ganglioside GM1 is localized in abundance at the node of Ranvier and serum IgM antibodies directed against the GM1 ganglioside are found in a proportion of the patients with MMN. These antibodies may play a pathogenic role in MMN by initiating or perpetuating the disease, but this is still poorly understood. From 1988 onwards, MMN has been increasingly recognized as a separate immune-mediated, and thus treatable, disease entity. Prednisolone and plasma exchange are ineffective in most patients with MMN. Some have claimed that of the immunosuppressants cyclophosphamide is effective, but it has major side-effects. In various placebo-controlled studies the effect of treatment with high-dose intravenous immunoglobulins (IVIg) in MMN has been proven, and IVIg treatment nowadays forms the standard treatment in MMN. Whether IVIg is effective in all stages of the disease, and especially in the long-term, has never been studied. The same holds true as regards the mechanisms of improvement. As IVIg treatment is expensive, and the frequent infusions may be burden-
Figure 2. Structure of a lower motor neuron.
some to patients, new treatment options are warranted in MMN. Over the last decade, the techniques to detect conduction block on nerve conduction studies and to measure serum anti-GM1 antibodies have been improved. Hereby patients with immune-mediated lower motor neuron syndromes, like MMN, can be distinguished from LMND. These new diagnostic possibilities of electrophysiological testing in motor neuropathies, together with those of genetic testing in LMND, have made some earlier studies of lower motor neuron syndromes obsolete and warrant an up-to-date classification.

**Aims of the study**

We first reviewed the existing literature to give an overview of the present knowledge of lower motor neuron syndromes (*chapter 2*).

The aims of our study were:

1. To improve the classification of patients with lower motor neuron syndromes by clinical analysis and by using the newest electrophysiological and genetic diagnostic tools:
   - the clinical and electrophysiological characteristics of sporadic LMND and a definition of clinical subtypes are described in *chapter 3*. Here we also propose a new classification of sporadic LMND.
   - the clinical and pathological features of two families with hereditary LMND forms and rapid progression are described in *chapter 5*.
   - mimic syndromes of sporadic LMND and an analysis of which features led to a revised diagnosis are described in *chapter 6*.
   - the clinical, laboratory and electrophysiological features of patients with multifocal motor neuropathy are described in *chapter 7*. Here we also propose new diagnostic criteria for MMN.
   - the clinical, electrophysiological, radiological and pathological features of patients with asymmetrical sensorimotor demyelinating neuropathy, not fulfilling diagnostic criteria for MMN or chronic inflammatory demyelinating polyneuropathy (CIDP), are described in *chapter 8*.

2. To determine the natural course of these lower motor neuron syndromes:
   - the results of a prospective study of the natural course of LMND are presented in *chapter 4*.
   - the results of a retrospective study of the natural course of MMN are presented in *chapter 10*. 
3. To describe MMN and to further explore disease mechanisms in MMN:
   • the distribution of electrophysiological abnormalities and the correlation with weakness was studied and from these data an optimal diagnostic protocol for MMN was designed, which is presented in chapter 9.
   • the results of a long-term study of muscle strength, disability and changes in motor nerve conduction in MMN during IVIg maintenance treatment are presented in chapter 11.
   • the results of an open pilot-study with interferon-β1a in MMN are presented in chapter 12.