Summary
This thesis focuses on patients with lower motor neuron syndromes, who have lower motor neuron (LMN) signs only. The aims of this study were first to improve the classification of patients with lower motor neuron syndromes using newest diagnostic methods, next to determine the natural course of these syndromes, and finally to further explore disease mechanisms in one of these syndromes, multifocal motor neuropathy (MMN).

A general introduction to lower motor neuron syndromes and the aims of the study are given in chapter 1. The group of patients with lower motor neuron syndromes is not well described and the various syndromes are relatively rare. New developments in DNA-proven hereditary lower motor neuron disease (LMND) and the differentiation of multifocal motor neuropathy (MMN) from LMND by nerve conduction studies, have made some of the earlier classifications of lower motor neuron syndromes obsolete. Also little is known about the natural course and treatment of lower motor neuron syndromes. In chapter 2 the literature of amyotrophic lateral sclerosis (ALS), hereditary and sporadic forms of LMND and of MMN is reviewed.

In chapter 3 we studied the clinical and electrophysiological features of 49 patients with sporadic adult-onset LMND in a cross-sectional study. Disease duration was more than four years, to exclude the majority of patients with ALS. Based on the pattern of weakness, we identified four groups: 13 patients with generalized weakness (group 1, slowly progressive spinal muscular atrophy), 8 patients with symmetrical, distal weakness (group 2, distal spinal muscular atrophy), 14 patients with non-generalized, asymmetrical, distal weakness of the arms (group 3a, segmental distal spinal muscular atrophy) and 14 patients with non-generalized, asymmetrical, proximal weakness of the arms (group 3b, segmental proximal spinal muscular atrophy), the latter two groups with disease progression to adjacent spinal cord segments. Distinctive features of group 1 were an older age at onset, more severe weakness and muscle atrophy, lower reflexes, greater functional impairment, more widespread abnormalities on concentric needle electromyography (EMG), respiratory insufficiency and serum M-protein. In groups 2, 3a and 3b, concentric needle EMG findings also suggested a more widespread disease process. Retrospectively, the prognosis of sporadic adult-onset LMND appears to be favourable, because clinical abnormalities were still confined to one limb in most patients after a median disease duration of 12 years. The described clinical phenotypes may help to distinguish between different LMND forms.

In chapter 4 we describe the results of a prospective study on 35 patients with LMND. Disease duration was more than four years and the follow-up period was 18 months. In the group as a whole, we found a significant decline of muscle strength and a significant increase of functional impairment and the number of affected limb regions. Per group, the decline of muscle strength and the increase of functional
impairment were significant and most pronounced in the patients with slowly pro-
gressive spinal muscular atrophy, but were also significant for patients with segmen-
tal distal spinal muscular atrophy and segmental proximal spinal muscular atrophy.
During or shortly after follow-up, respiratory function worsened in four of the nine
patients with slowly progressive spinal muscular atrophy. In one of these patients
upper motor neuron (UMN) signs developed and the diagnosis was changed in ALS
and in another patient the diagnosis familial ALS was made, as the sister of this
patient developed bulbar ALS. Also in one patient with segmental proximal SMA
hyperreflexia developed and the diagnosis ALS was made. The natural course of
sporadic adult-onset LMND therefore appears slowly progressive, life expectancy
may be decreased and UMN signs may develop. Thus, these disease forms show
overlap with ALS. Until now, there are no clinical or laboratory findings that early
in the disease course distinguish LMND forms from ALS, or slowly progressive
from rapidly progressive LMND forms. These results will be helpful in making a
correct diagnosis in these patients after a prolonged observation.

In chapter 5 we describe two families, with each three family members, with a hered-
itary form of LMND with adult onset and rapid progression. No involvement of
upper motor neurons was found either clinically or pathologically. Disease progress-
sion was rapid as the majority of patients died from respiratory failure within one to
five years after onset of disease. On pathological examination of the spinal cord we
found ballooned neurons, neuronophagia and gliosis in family A, that have been
regarded as characteristic pathological features of infantile-onset spinal muscular
atrophy (SMA). In family B specific neuronal changes were observed that also occur
in patients with ALS. An autosomal dominant mode of inheritance would seem
likely in both families. In family A the pathological findings and the clinical presen-
tation with symmetrical proximal limb weakness show similarities with autosomal
dominant SMA. Because of the pathological features, the distal asymmetrical muscle
weakness, the bulbar signs, and a high age at onset in family B, we hypothesize that
this family has suffered from familial ALS (FALS). The disease forms in both families
further broaden the spectrum of LMND.

Several clinically less disastrous or even treatable diseases can mimic early ALS or
LMND. In chapter 6 we describe 17 out of 89 patients of our prospective study of
LMND, in whom after an extensive work-up another diagnosis than LMND was
established. In 11 of the 17 patients a potential treatment was available. These diag-
noses include: MMN (7), chronic inflammatory demyelinating polynuropathy
(CIDP) (2), inflammatory myopathy (1), myasthenia gravis (1). The remaining six
patients were diagnosed as having myopathy, syringomyelia, slowly progressive ALS,
chronic idiopathic axonal polynuropathy, lumbar disk herniation or idiopathic
brachial plexus neuropathy. The two most common reasons for diagnostic revision
were the development of atypical symptoms, the results of ancillary investigations, or a combination of both. This study shows that patients with LMND should be followed up meticulously and that additional investigations should be performed, especially electrophysiological examination, in order to make a correct diagnosis and to identify potentially treatable syndromes.

As multifocal motor neuropathy (MMN) is a potentially treatable disorder, its differentiation from LMND is important. Evidence of conduction block is considered one of the relevant criteria for the diagnosis of MMN. However, strict criteria for conduction block may lead to underdiagnosis of MMN. In chapter 7 we studied the clinical, laboratory and electrophysiological characteristics of 37 patients presenting with a lower motor neuron syndrome and electrophysiological features compatible with demyelination. We propose a set of clinical, laboratory and electrophysiological criteria for the diagnosis of MMN, which has been verified by follow-up and response to treatment with intravenous immunoglobulins (IVIg). Using these criteria, 21 patients were diagnosed as definite MMN (17 responders), seven patients as probable MMN (5 responders) and nine as possible MMN (1 responder). Age at onset, the number of affected limb regions and the number of patients with CK >180 U/L were significantly lower in responders than in non-responders. Elevated anti-GM1 antibodies and definite conduction block were found significantly more often in responders. The proposed diagnostic criteria may be useful in clinical practice and therapeutic trials.

Several patients have been reported with an asymmetric sensory or sensorimotor demyelinating neuropathy not fulfilling the diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) or MMN. In chapter 8 we present the clinical, electrophysiological, radiological and pathological features of six patients with such a neuropathy. All six patients were initially affected in only one limb and in four patients the neuropathy progressed to other limbs in an asymmetrical fashion over a number of years. On electrophysiological examination, evidence of multifocal demyelination and conduction block in motor and sensory nerves was found in all patients. MR-imaging of the brachial plexus revealed swollen nerves and an increased signal intensity on T2-weighted imaging in four patients. A biopsy taken from the brachial plexus of one patient revealed evidence of inflammation. All patients showed a beneficial response to IVIg treatment. Thirty-four similar patients have been reported previously, many of whom were initially diagnosed as having various other non-treatable diseases. We propose calling this neuropathy multifocal inflammatory demyelinating neuropathy (MIDN) and considering it as a distinct clinical entity to facilitate early diagnosis of this treatable disorder.

In chapter 9 we present the results of a study on the distribution of electrophysiological abnormalities and its correlation with weakness in 39 patients with MMN, who
underwent an extensive standardized electrophysiological examination, and discuss whether these results are relevant for the development of optimal electrodiagnostic protocols. We found a preferential localisation of demyelinating features in long arm nerves and of axonal loss in longer (more often leg than arm) nerves. Weakness was associated with features of demyelination and axonal loss in arm nerves, and with features of axonal loss in leg nerves. For the arm nerves, it is possible that the length dependence of axonal loss is due to the random distribution of demyelinating lesions that lead to axonal degeneration. However, a substantial number (approximately one-third) of electrophysiological abnormalities was found in nerves innervating non-weakened muscles. These results imply that in MMN, conduction block is most likely to be found in long arm nerves innervating weakened muscles, but if conduction block cannot be detected in these nerves the electrophysiological examination should be extended to other arm nerves including those innervating non-weakened muscles.

The majority of patients with MMN respond to IVIg treatment. A prospective study on the natural course of MMN is therefore not feasible. In chapter 10 we retrospectively describe the course of the disease in 38 patients with MMN, in whom disease duration ranged from 6 months to 34 years. Disease severity was assessed by determining muscle weakness, disability, conduction block, and distal and proximal compound muscle action potential (CMAP)-amplitude. As indicator for an ongoing immune-mediated process, the response to one course of IVIg treatment was measured in 34 patients and associated with disease severity. With increasing disease duration, weakness and disability became significantly more severe, and the distal and proximal CMAP-amplitude decreased significantly. The number of conduction blocks was significantly higher in patients with a disease duration longer than 10 years than in those affected less than 10 years. Thirty of the 34 patients responded to IVIg treatment. Non-responsiveness to IVIg was not associated with any of the disease variables. Severe and widespread weakness was significantly associated with a response ≥ 2 on the MRC-sumscore. Our results provide evidence for a slowly progressive disease course of MMN. The good response to IVIg treatment in patients with severe and prolonged disease indicates that progression may be the result of an ongoing immune-mediated process. These findings imply that early treatment may prevent future progression of weakness and disability in patients with MMN.

As the effect of IVIg treatment in MMN lasts only several weeks, IVIg maintenance treatment is often necessary to maintain the effect on muscle strength. As IVIg maintenance treatment is expensive, and the frequent infusions may be burdensome to patients, it is important to know whether IVIg maintenance treatment is effective in the long-term. The results of a long-term follow-up study of 11 patients with MMN, who received IVIg maintenance treatment for a period of 4 - 8 years, are
presented in chapter 11. During follow-up, the frequency and dosage of IVIg infusions, muscle strength (MRC grading and hand-held dynamometry of a selection of weak muscle groups), systematic electrophysiological studies, and upper and lower limb disability were assessed. The frequency and dosage of IVIg infusions ranged from one infusion every 1 to 7 weeks and an average dosage of 7 to 48 g per week. Muscle strength improved significantly within three weeks of the start of IVIg treatment, and was still significantly better at the last follow-up examination than before treatment, even though it decreased slightly, and significantly, during follow-up. Upper limb disability was significantly better after the first full course of IVIg than before treatment. Conduction block disappeared in six nerve segments but new conduction block appeared in eight nerve segments during the follow-up period. Changes consistent with improvement (‘remyelination’ or ‘reinnervation’) occurred in 13 nerves during follow-up and changes consistent with worsening (‘demyelination’ or ‘axonal loss’) occurred in 14 nerves. Electrophysiological changes consistent with improvement were significantly associated with the presence of conduction block before IVIg treatment. Thus, IVIg maintenance treatment has a beneficial long-term effect on muscle strength and upper limb disability but may not prevent a slight decrease in muscle strength. The electrophysiological findings imply that IVIg treatment favorably influenced mechanisms of remyelination or reinnervation but that axonal loss cannot be prevented.

As new treatment strategies are warranted in MMN, we performed an open pilot-study with 22 µg interferon-β1a (IFN-β1a), which has been shown to be effective for multiple sclerosis, in nine patients with MMN and describe the results in chapter 12. All patients were treated with IFN-β1a for six months (3x/wk) and had previously shown a good response to IVIg treatment. Five patients received IVIg maintenance therapy which was stopped prior to the study. Muscle strength, disability and electrophysiological examination were evaluated. In six patients there was no effect of treatment with IFN-β1a. Four of these patients deteriorated in such a way that IVIg had to be restarted during IFN-β1a treatment. Three patients showed an improvement on IFN-β1a which was more pronounced than on IVIg in the majority of the affected muscle groups and which sustained itself for months after discontinuation of IFN-β1a. In the patients who showed improvement, muscle strength was not severely impaired, disease duration was relatively short and conduction block and temporal dispersion occurred less often. Side-effects of IFN-β1a were moderate, and gradually disappeared after several weeks of treatment. Based on these results, a controlled study is necessary to further investigate the effect of IFN-β1a treatment in patients with MMN, including newly diagnosed patients with a relatively short disease duration.
The results of the studies in this thesis are discussed in chapter 13. The pathogenesis of sporadic LMND and the precise pathophysiological and immunological mechanisms of MMN are largely unknown. Until we have identified these possible underlying pathophysiological mechanisms it will prove difficult to consider the various lower motor neuron syndromes as separate diseases. Because diagnostic and therapeutic options may differ, it seems rational to consider them as a spectrum of syndromes, which can be distinguished from each other on the basis of the clinical presentation and the laboratory and electrophysiological features. For the individual patient distinction between the various syndromes is important as it enables the physician to provide adequate information over the disease course, and to facilitate early treatment with either riluzole in selected syndromes or with IVIg or IFN-β1a in MMN and MIDN. To conclude, further studies are needed to unravel pathophysiological mechanisms, identify possible susceptibility factors, determine prognostic factors and search for treatment options in patients with lower motor neuron syndromes.