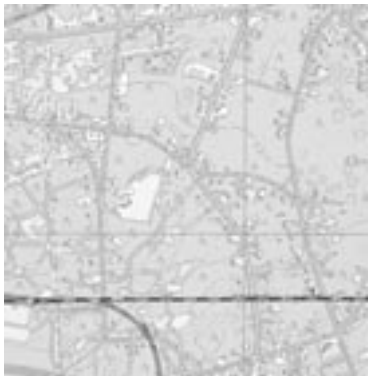
The spectrum of lower motor neuron syndromes

classification, natural course and treatment



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The spectrum of lower motor neuron syndromes
classification, natural course and treatment

Het spectrum van aandoeningen van perifeer gelegen motorische neuronen
classificatie, natuurlijk beloop en behandeling

(met een samenvatting in het Nederlands)

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Voor mijn ouders

Voor Herman, Philippe en Vincent

Contents

"The spectrum of lower motor neuron syndromes: classification, natural course and treatment"

Background

This thesis focusses on patients with lower motor neuron syndromes. This relatively rare group of syndromes is clinically not well described and the pathogenesis is largely unknown. Two subgroups can be distinguished: patients in whom motor neurons (lower motor neuron disease (LMND)) or motor axons and their surrounding myelin (multifocal motor neuropathy (MMN)) are affected, both leading to muscle atrophy and weakness. As MMN is a potentially treatable disorder, its differentiation from LMND is important. Evidence of motor conduction block on nerve conduction studies and a positive response to treatment with intravenous immunoglobulins (IVIg) are considered the most relevant criteria for the diagnosis of MMN. The improvement of the techniques to detect conduction block and new developments in DNA-proven hereditary LMND, 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.

Aims

The aims of this study were (1) to improve the classification of patients with lower motor neuron syndromes using newest diagnostic methods, (2) to determine the natural course of these syndromes, and (3) to study treatment forms in MMN.

Methods

Patients were examined clinically at a regular basis, which consisted of the assessment of muscle atrophy and weakness, respiratory function and functional impairment. All patients underwent an extensive, standardized electrophysiological examination at least once.

Results

Based on the pattern of weakness in 49 patients with LMND, we identified four subgroups. Except for one group with generalized weakness and respiratory insufficiency, leading to death in one third of patients, the disease course in patients with

LMND was slow, with minimal progression of muscle weakness and functional impairment over years. Also in patients with MMN we found evidence for a slowly progressive disease course.
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 IVIg treatment in 37 patients with a lower motor neuron syndrome. Additionally, we studied the distribution of electrophysiological abnormalities in MMN, its correlation with weakness and the development of an optimal electrodiagnostic protocol for MMN.
The results of a follow-up study on the efficacy of long-term (4-8 years) maintenance therapy in 11 patients with MMN, showed that IVIg maintenance treatment has a beneficial long-term effect on muscle strength and upper limb disability, and thus seems rational, but may not prevent a slight decrease in muscle strength. Electrophysiologically, both improvement and worsening were found. In an open pilot-study with interferon-b1a (IFN-b1a, 3x/wk for 6 months) in nine patients with MMN, three patients showed an improvement on IFN-b1a which was more pronounced than on IVIg and which sustained itself for months after discontinuation of IFN-b1a. A controlled study is necessary to further investigate the effect of IFN-b1a treatment in patients with MMN.

Conclusions

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 electrophysiological findings. 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 in MMN.

Keywords

Lower motor neuron disease, motor neuron disease, amyotrophic lateral sclerosis multifocal motor neuropathy, neuropathy, chronic inflammatory demyelinating polyneuropathy, intravenous immunoglobulins.

Nederlandse Basisclassificatie: 44.90 Geneeskunde, neurologie

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.

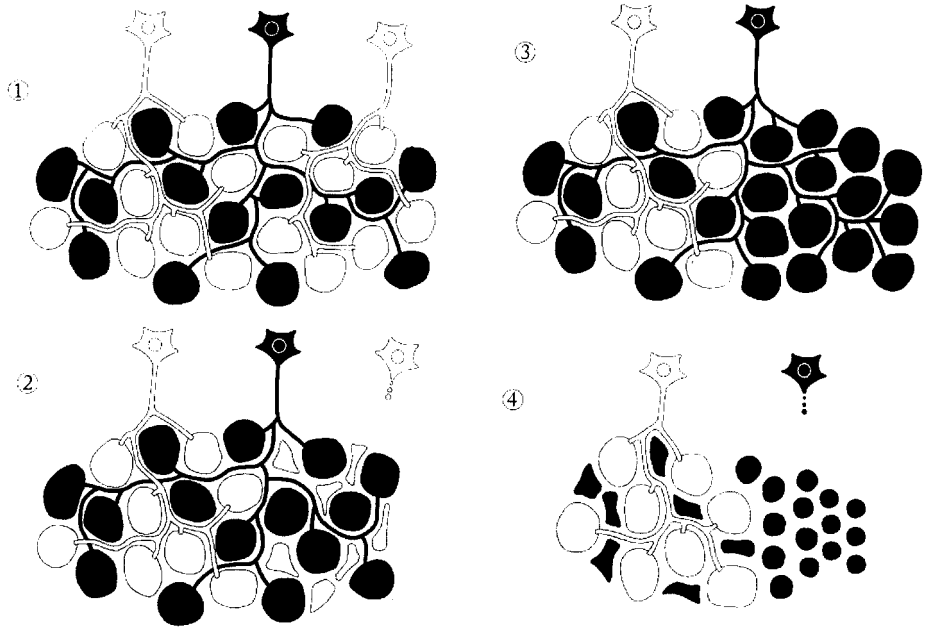

Figure 1. Schematic representation of various stages of chronic denervation and reinnervation. 1.1 Three motor units, two type 1 units (light) and one type 2 (black). 1.2 Degeneration of one motor neuron leads to atrophy of all muscle fibers of the corresponding motor unit. 1.3 Successful reinnervation by collateral sprouts from a nearby intramuscular axon. The mosaic pattern is replaced in part by a group of histochemically uniform type 2 fibres (type grouping). 1.4 Ongoing degeneration of motor neuron cells leads to denervation and atrophy of all muscle fibers of the enlarged motor unit (grouped atrophy). Other atrophic fibres belonging to the same motor unit lie disseminated between non-atrophic fibres and are candidates for reinnnervation by axon branches of surviving motor neurons.

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.[25,85,152,157] 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.[6] 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 GM1ganglioside 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-

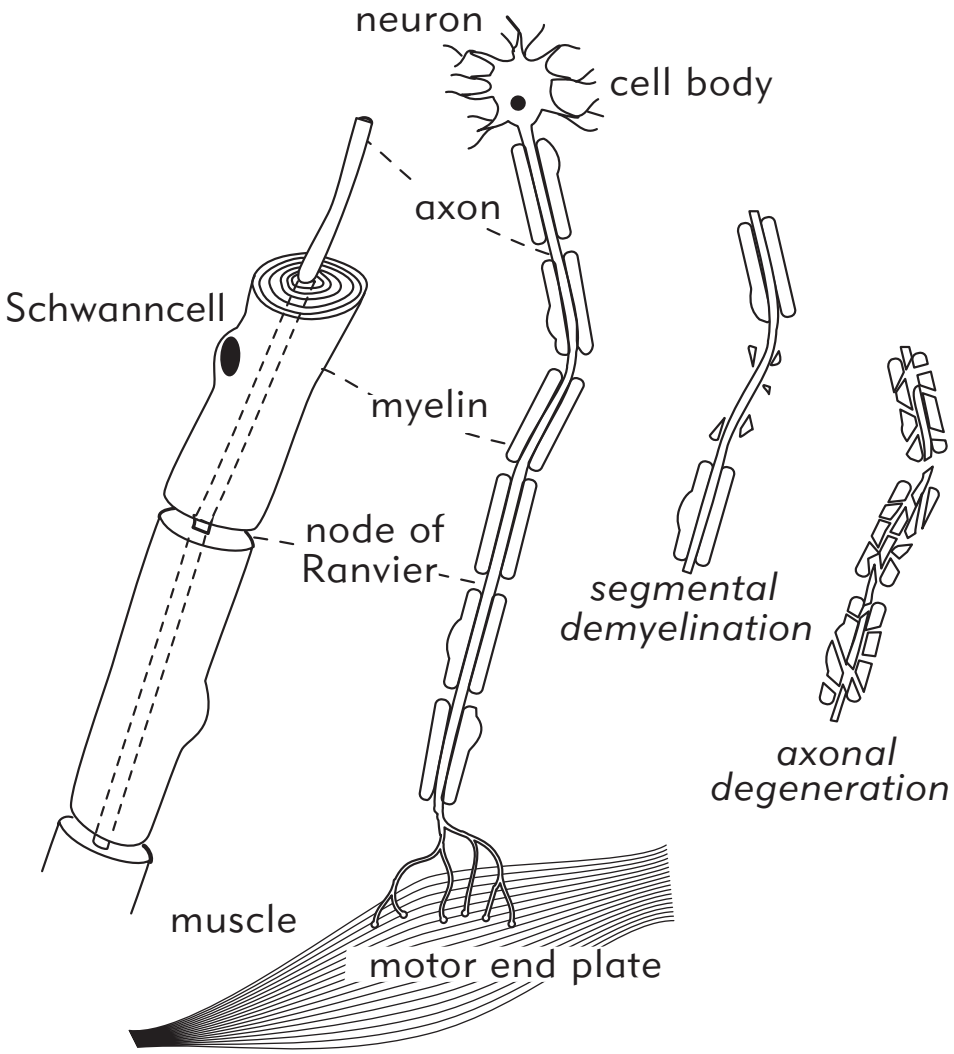

Figure 2. Structure of a lower motor neuron.

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*.

Review of the literature

In this chapter subsequently the literature of amyotrophic lateral sclerosis (ALS), hereditary lower motor neuron disease (LMND), sporadic LMND and multifocal motor neuropathy (MMN) is reviewed. Table 1 gives a survey of the various lower motor neuron syndromes that will be discussed.

Table 1. The spectrum of lower motor neuron syndromes

Hereditary forms
Proximal childhood spinal muscular atrophy with SMN gene mutation (types I -III)[s, p]
Proximal adult-onset spinal muscular atrophy (type IV)[s, p]
Kennedy disease (bulbospinal muscular atrophy)[s, p, b]
Syndrome of Brown-Vialetto-Van Laere[b]
Syndrome of Fazio-Londe (infantile progressive bulbar palsy)[b]
Lower motor neuron variant of familial ALS[s, d, b]
Distal spinal muscular atrophy[s, d]

Sporadic forms
Progressive spinal muscular atrophy[a, d]
Hirayama disease[a, d]
Scapulohumeral spinal muscular atrophy[a, p]
Monomelic amyotrophy of lower limb[a, d]
Post-polio syndrome[a]
Radiation lower motor neuron syndrome[a]

Immune-mediated forms
Multifocal motor neuropathy[a, d]

Lower motor neuron involvement (fasciculations, muscle cramps, atrophy and weakness) is present in the limbs and distributed asymmetrically (a), symmetrically (s), and the limbs are predominantly distally (d) or proximally (p) affected. When bulbar signs and symptoms predominate the clinical picture (b).

1 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common and well-recognized of the motor neuron diseases. In ALS, both upper (cortical) motor neuron (UMN) signs and lower (brainstem and spinal cord) motor neuron (LMN) signs are found (table 2). The incidence of ALS around the world is about 2 : 100.000.[218] It also is the most severe form, causing death from respiratory failure within a few years. The median survival time from onset of symptoms is 29 months.[85] Approximately 10% of patients survive for more than 10 years after diagnosis. In 75% of patients, the first symptoms are in the limbs, with the arms and legs equally affected. Twenty-five % of patients present with bulbar symptoms. Bulbar onset is more common in women than in men and in older individuals than in younger individuals. It is also associated

Table 2. Upper and lower motor neuron signs

Upper motor neuron signs
spasticity
decreased dexterity
hyperreflexia and pathological reflexes
muscle weakness
Lower motor neuron signs
fasciculations
muscle cramps
muscle atrophy
muscle weakness
loss or diminution of reflexes

with significantly reduced survival, with a median survival of about 20 months. The age at onset is another prognostic factor, with shorter survival in patients with a relatively high age at onset. In most patients, age at onset ranges between 57 and 60 years.[85] In less than 5% of patients disease onset is before the third decade and in approximately 10% of patients in the seventh or eight decade. Males are more frequently affected than women in a proportion of 1.3 : 1, until in the seventh decade, when the rates become equal. The El Escorial World Federation of Neurology criteria for the diagnosis of ALS established at a conference of experts in 1990 and recently revised, emphasise the presence of LMN and UMN signs in several body regions (**www.wfnals.org**) (table 3). Because ALS is a devastating and fatal disease, a correct diagnosis is very important.

Table 3. El Escorial Revised Criteria for the Diagnosis of ALS

Definite ALS
UMN signs and LMN signs in 3 regions
Probable ALS
UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs
Possible ALS
UMN signs and LMN signs in 1 region (together), or
UMN signs in 2 or more regions, or
UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs
Probable ALS – Laboratory supported
UMN signs in 1 or more regions and LMN signs defined by EMG criteria in at least 2 regions

UMN = upper motor neuron. LMN = lower motor neuron. If only fasciculations: search with electromyography for active denervation. Regions reflect neuronal pools: bulbar, cervical, thoracic, lumbosacral.

2 Hereditary forms of LMND

SMN gene linked childhood spinal muscular atrophy (SMA)

Before the discovery of the mutations in the survival motor neuron (SMN) gene on chromosome 5 underlying AR inherited SMA, three types were distinguished. For the clinic this classification is still valuable (table 4).[83,247]

Table 4. Classification of hereditary proximal spinal muscular atrophy

Type I (Werdnig-Hoffmann disease)
1. onset < 6 months (may be antenatal)
2. never able to sit
3. death form respiratory insufficiency < 2 years

Type II (intermediate type)
1. 6 months > onset < 18 months
2. never able to stand
3. shortened life expectancy

Type III (Kugelberg-Welander disease)
1. 18 months > onset, rarely at young adult age
2. SMA IIIa manifests before the age of 3 years, SMA IIIb thereafter
3. able to stand without help
4. gradual loss of function
5. variable handicap
6. life expectancy normal

Type IV Adult-onset spinal muscular atrophy
1. several phenotypes (proximal, distal and generalized weakness)
2. autosomal recessive + autosomal dominant inheritance
3. rapid progression may occur (see § 3.3)

SMA type I, Werdnig-Hoffmann disease, is a disastrous disease. Symptoms may present before birth as reduced child movements. Newborns may show arthrogryposis. After birth, hypotonia, weakness and respiratory or swallowing difficulties are the presenting symptoms. The incidence of SMA type I is 1 : 100.000, making SMA I the most frequent hereditary disease leading to death in the first year of life. SMA II and III are less frequent. In both SMA forms muscle weakness is symmetrical and proximal and affects the legs more than the arms, leading to a limb girdle pattern of weakness. Tremor of the hands is often seen. The muscle stretch reflexes are diminished or absent. In SMA II progressive scoliosis may occur as length growth accelerates. Age of onset predicts disability in SMA type III.[188,247] Fifty percent of patients with onset between two and six years were able to walk without support at the age of 44 years. If onset was before the age of two years, half of the patients could no longer walk without support at the age of 12 years.

The genetics of SMA

The large SMA locus on chromosome 5 contains at least two copies of three genes: the SMN gene, the neuronal apoptosis inhibitory protein (NAIP) gene and the p44 gene. Ninety-five percent of all SMA type I - III patients show deletions of exon 7 or exons 7 and 8 in the SMN genes on both chromosomes. NAIP gene deletions were found in 37% of patients in an affected Dutch population.[33] Incidentally, homozygous deletions of the telomeric SMN gene have been found in some healthy sibs of SMA patients, with minor complaints of frequent muscle cramps.[21] Therefore, these mutations alone cannot explain phenotypes. The complexity of the SMA locus may hold the clue to the explanation of phenotypic differences in SMA. It has been demonstrated that deletions in the telomeric copies of the SMN gene (SMN1 gene) cause SMA. The centromeric SMN gene (SMN2 gene) may encode for some SMN protein. In patients with SMA, several copies of the SMN2 gene can be found. Patients with SMA type I have two or three copies, patients with SMA type III have four. This suggests that the SMN2 gene is translated into an at least partially functional protein that protects against loss of motor neurons and modulates the phenotype of SMA.[16,126] In addition, in a recent study an overrepresentation of homozygous SMN2 gene deletions in patients with ALS has been reported.[239] The presence of a SMN2 gene deletion was independently associated with a shorter survival time. Thus, in sporadic ALS the SMN2 gene mutations could act as a modifier of phenotype, both as risk factor and as factor influencing prognosis. These findings provide new insights in the understanding of the pathogenesis of SMA and ALS. Future knowledge of the function of the SMN protein and other proteins involved could lead to new treatment strategies.

Adult-onset forms of hereditary spinal muscular atrophy

Adult-onset proximal SMA with autosomal recessive (AR) and autosomal dominant (AD) inheritance are both known as SMA type IV. Cases with AR inheritance and mutations in the SMN1 gene have been incidentally reported[17], but until now the SMN1 gene has not been systematically studied in these patients. In individual patients, the disease history must reveal whether symptoms and signs developed after the second decade. It would be exciting to analyze the SMN2 gene also in these patients (see § 3.2). In the original description by Pearn, approximately 30% of adult-onset SMA patients were considered to have AD inheritance. Adult-onset AD SMA may manifest in the third or fourth decade with slowly progressive proximal muscle weakness. Patients lose the ability to run within five years of onset, and life expectancy is probably shortened, but not dramatically as a median life expectancy of 20 years was observed.[172] However, families have been described with signs and

symptoms of severe and progressive lower motor neuron syndromes of possible AD inheritance, leading to death within a few years after the onset of symptoms.[98]

Kennedy disease (bulbospinal muscular atrophy)

In 1968, Kennedy described ′progressive proximal spinal and bulbar muscular atrophy of late onset′ with X-linked inheritance in 11 members of two families.[113] Later, this disease form became known as Kennedy disease. At young adult age muscle cramps and fasciculations may occur, but usually Kennedy disease manifests after the fourth decade with a limb-girdle pattern of muscle atrophy and weakness. Facial weakness, dysarthria and dysphagia are prominent features. Atrophy of the tongue and fasciculations in the perioral muscles are frequently observed. Some patients show a postural tremor of the hands. UMN signs are absent. Sensation is normal, but abnormal sensory action potentials are found at electrophysiological examination. Progression is slow. In severely affected patients dysphagia and respiratory insufficiency can affect life expectancy. Fifty percent of the affected men show signs of partial androgen insensitivity and reduced fertility with testicular atrophy, gynaecomastia, oligo- or azoospermia, slightly elevated serum gonadotropin levels and glucose intolerance. Kennedy disease is a well-known ALS-mimic.[64,219]
Kennedy disease is caused by an expansion of CAG trinucleotide repeats in the androgen receptor gene. The gene encodes for the aminoacid glutamin. Healthy controls have 21 - (maximal) 37 repeats, whereas patients show expansions of 38 - 62 repeats. The presence of the expanded polyglutamin is postulated to act through a pathogenetic mechanism that is associated with a gain of function in the involved proteins.[134] Female carriers may show some clinical abnormalities, like mild muscle weakness, frequent muscle cramps, slight elevation of creatine kinase level, or neurogenic changes on electromyography.[95]

Syndrome of Brown-Vialetto-Van Laere

In the Brown-Vialetto-Van Laere syndrome cranial nerve palsies occur, together with sensorineural deafness. Presentation is usually in the first or second decade, and progressive bulbar weakness may be associated with limb weakness, brisk lower limb reflexes and respiratory insufficiency. A variety of other neurological features have occasionally been noted including ataxia, optic atrophy, retinitis pigmentosa, epilepsy and autonomic dysfunction. The inheritance is possibly AR, but males are reported to be more severely affected. The prognosis is variable. In some patients the disease rapidly leads to death from respiratory insufficiency, whereas in others the disease course was slowly progressive.[194,215]

Syndrome of Fazio-Londe (infantile progressive bulbar palsy)

Progressive bulbar paralysis due to depletion of the neurons in the cranial motor nuclei with subsequent loss of anterior horn cells in the upper cervical cord is a rare variant of SMA. This condition, sometimes denominated as the Fazio-Londe syndrome, occurs in children between 1 and 12 years and presents with stridor, palatial palsy, facial weakness and dysphagia.[215] Ophthalmoplegia is also reported. Some cases appear to be inherited in an AR fashion. Life expectancy is determined by respiratory function, and often the disease is fatal within two years after onset.[44]

Familiar ALS with predominant lower motor neuron signs

ALS is familiar in about 5 - 10% of patients and is almost always inherited as an AD trait. In 25% of patients with familiar ALS a mutation in the superoxide dismutase (SOD1) gene can be found. Until now, more than 90 different mutations have been identified.[164] Some mutations are associated with particular phenotypes, with onset varying from in the third to the seventh decade and a slowly to rapidly progressive disease course. In North America the most common mutation is a substitution of valine for alanine at position four in SOD1 (A4V). Interestingly, these patients present with predominant LMN signs in the third to fifth decade. The disease course is progressive as the mean life expectancy is approximately one year after the onset of symptoms.[100,184] Pathological examination also revealed evidence of predominant LMN involvement with sparing of Betz cells and only mild changes in the corticospinal tracts.[38]

Distal spinal muscular atrophy

The syndrome of distal spinal muscular atrophy with symmetrical distal muscle weakness in arms and/or legs is genetically heterogeneous. Harding analyzed all 78 cases described in the literature, including her own series of 34, and found that 41 patients were sporadic, in 29 patients the pattern of inheritance was AD and in 8 AR.[79] Sporadic cases have thus usually been described under the heading of hereditary distal spinal muscular atrophy.[79,138,140] Ages of onset may vary between 5 and 70 years.[197] Nevertheless, the clinical picture of distal spinal muscular atrophy is fairly homogeneous. Slowly progressive symmetrical muscle weakness and atrophy involve legs and feet first. After many years, the hands and, later, the forearms are affected. Distal spinal muscular atrophy should be differentiated from hereditary motor and sensory neuropathy (HMSN) type 2, the neuronal variant of Charcot-Marie-Tooth disease - CMT 2, in which clinical sensory loss is not always evident. Features which distinguish between distal spinal muscular atrophy and HMSN type 2 are more common upper limb weakness[80] and low or absent sensory action potentials in HMSN type 2.[77]

3 Sporadic forms of LMND

The sporadic forms of LMND form a heterogeneous group. Different forms have been described under various names. The studies that so far have been published, however, demonstrate a few methodological shortcomings. First, they have been published before the increase of diagnostic facilities (MRI, DNA-analysis of SMN and NAIP genes and the androgen receptor gene, advanced nerve conduction studies in search for conduction block and features compatible with demyelination). Second, publications often concern case-reports or retrospective studies of small groups of patients. Prospective studies of non-hereditary LMND are scarse.[30] In the following section six phenotypes will be discussed.

Progressive spinal muscular atrophy

In 1850 Aran reported of 11 patients with different patterns of muscle atrophy and weakness in the limbs. He introduced the term progressive muscular atrophy.[6] One year before, in 1849, Duchenne de Boulogne reported of electrophysiological characteristics of patients with arm weakness.[51] Hence the eponym Aran-Duchenne's disease is used for this form of LMND. The term progressive muscular atrophy is synonymously used with progressive spinal muscular atrophy, a term introduced by Müller in 1952.[152] Onset of muscle weakness occurs in distal arm or leg muscles. Most patients report atrophy. Onset is asymmetrical but at neurological examination bilateral involvement is usually observed. Fasciculations are not reported spontaneously. In affected limbs muscle stretch reflexes are depressed. The disease course of progressive spinal muscular atrophy is slow. Deterioration is noted over years to decades. In the course of the disease, proximal arm or leg muscles become affected and muscle weakness spreads to those limbs that were not affected before, also with distal muscles becoming affected earlier than proximal muscles. In the final stage respiratory muscles may become affected leading to respiratory insufficiency. Rarely, the bulbar motor neurons may become affected, leading to dysphagia and dysarthria, as well.

Only those few cases with continuing slow progression of purely LMN involvement may comprise progressive spinal muscular atrophy.[158] In some patients, however, rapid progression and appearance of UMN signs soon indicate a diagnosis of ALS. In two autopsy series of a total of 25 patients with progressive spinal muscular atrophy corticospinal tract involvement was demonstrated in 17 (68%).[20,124] It is now well established that ALS is pathologically characterized by the presence of ubiquinated inclusions in lower motor neurons of brain stem and spinal cord. Ubiquinated inclusions were also demonstrated in lower motor neurons of patients with progressive spinal muscular atrophy.[94] Therefore, most cases of progressive spinal muscular atro-

phy seem to be pathologically linked to ALS. The question whether these patients suffer from a distinct disease entity or a subtype of ALS has not been answered yet. Factors that determine disease progression in progressive spinal muscular atrophy are unknown. SMN 2 gene analysis has so far been performed in two small groups of patients with progressive spinal muscular atrophy. In both studies deletions were found in 36% of patients (versus 5% in the normal population). However, both groups may not be comparable as disease progression varied from slow[56] to comparable with that of ALS.[149] Nevertheless, SMN 2 may act as a susceptibility factor, increasing the risk of developing adult-onset lower motor neuron degeneration.

Hirayama disease

In 1959 Hirayama described a condition, which has also been known as juvenile muscular atrophy of distal upper extremity. Predominantly young men are affected.[89] Onset is insidious and characterized by atrophy and weakness in muscles of one hand and forearm. The brachioradialis muscle is often spared (oblique amyotrophy). Many patients report that the weakness aggravates in a cold environment (cold paresis) and improves in a warm environment. In most patients symptoms and signs are unilateral. In about one third of patients less pronounced contralateral involvement of hand and forearm is reported. A minority of patients show weakness in triceps, biceps or even deltoid muscles at the first affected side.[206] No fasciculations are seen with the hand at rest, but weak finger extension may cause fascicular twitching of the forearm muscles and also tremulous movement of the fingers. Muscle stretch reflexes are usually normal, and rarely brisk in the affected limb. Initial progression over months to years is often followed by a spontaneous arrest. The pathogenesis is unknown. Hirayama performed MRI studies showing some forward displacement and flattening of the lower cervical spinal cord during neck flexion in 87% of 49 patients, whereas this was found in none of the control subjects.[88] This suggests that a mechanical force may be a causative factor.

Scapulohumeral muscular atrophy

The syndrome of unilateral proximal weakness in the scapulohumeral region is less well known. Both Kaeser and Katz previously reported on this form of LMND.[102,110] They described mainly male patients with unilateral muscle weakness and wasting in shoulder and upper arm muscles of essentially the C5 and C6 myotomes. After years spreading of weakness to the contralateral shoulder was reported. Most patients had complaints of leg muscles and a minority of neck muscles. Bilateral proximal weakness could result in a 'neurogenic man-in-the-barrel syndrome phenotype'. This condition resembles the flail-arm phenotype that has been described in a subgroup of patients with ALS.[91] However, these latter patients

often show a progressive disease course that rapidly leads to death, while in patients with scapulohumeral muscular atrophy respiratory insufficiency has not been reported.

Monomelic amyotrophy of lower limb

Most patients with unilateral muscular atrophy restricted to one leg have been reported in India[72,178], with only few cases reported in the western world.[45,46] Characteristic clinical features of this form of LMND are muscle atrophy and weakness of one leg. Onset is insidious, and may be difficult to date precisely. The majority of affected patients are male. In half of the cases there is uniform diffuse wasting of the whole leg. In a quarter of patients wasting is localized to the muscles below the knee. The quadriceps femoris muscle alone is affected in a minority of patients. Atrophy is often out of proportion compared with weakness. Interestingly, disability is minimal. In all patients the disease course is initially slowly progressive, followed by a stationary period of decades without any clinical sign of spreading.[178]

Post-polio syndrome

The term post-polio syndrome is used to describe new neuromuscular complaints which patients may experience decades after recovery from paralytic poliomyelitis. Complaints include new or increasing muscle atrophy and/or weakness, cramps, muscle and joint pains, fasciculations, fatigue, diminished endurance and increase of disabilities. It was suggested that there are two distinctive groups of patients. The first group manifested new atrophy and/or weakness in previously affected or clinically unaffected muscles. These patients may suffer from progressive post-poliomyelitis muscular atrophy. The second group had new neuromuscular complaints but no new weakness.[41] However, in clinical perspective distinction between patients with or without progressive muscular weakness is not always easy, as the reported decrease in muscle strength can not always be confirmed by muscle strength assessment.[96] Therefore, the term post-polio syndrome now describes the whole spectrum of new symptoms reported by polio survivors, after other causes of progressive neuromuscular symptoms have been excluded. The pathogenesis of the syndrome is unsolved. Polio survivors, who are supposed to have a motor neuron population that is reduced in size, may be more susceptible to motor unit insufficiency. At older age, the loss of relatively few giant motor units may result in a disproportionate loss of muscle strength.

Radiation lower motor neuron syndrome

This rare syndrome is a delayed complication of irradiation of the spinal cord, mainly in the pelvic region, and should be distinguished from delayed radiation myelopa-

thy, that often presents as a Brown-Séquard syndrome. Months to years following irradiation, patients develop a subacute flaccid, often asymmetrical paraparesis of the legs, that affects both distal and proximal muscles and is accompanied by atrophy, fasciculations and areflexia. There is no sensory disturbance or sphincter dysfunction. The myelogram and MRI are normal. On electromyography, denervation is found, but sensory and motor conduction velocities are normal. The deficit usually stabilizes after several months to years, often while the patient is still able to walk. Pathological reports describe degeneration of cauda equina roots with chromatolysis of anterior horn cells, suggesting secondary damage.[177]

4 Multifocal motor neuropathy

MMN is a rare condition, characterized by slowly progressive asymmetrical weakness and atrophy of limb muscles without sensory loss.[130,170,176,185] Patients with MMN are often diagnosed as having LMND or even ALS initially.[219] It is important to recognize patients with MMN as it is a treatable condition and, in contrast with ALS, compatible with normal longevity. MMN can be differentiated from ALS and LMND by the finding of persistent motor nerve conduction block on nerve conduction studies outside nerve compression sites. Evidence of motor conduction block is considered the electrodiagnostic hallmark of MMN (figure 1). Therefore, in all patients with pure lower motor neuron syndromes extensive electrophysiological analysis in search for conduction block is required.

Once appreciated, the clinical picture of MMN is very characteristic. Usually muscles of the lower arm and hand are affected first and symptoms and signs of these muscles prevail for a long time. Muscle atrophy and weakness is often distributed asymmetrically. Fasciculation and cramps are present in about two thirds of the patients. Tendon reflexes are usually reduced in affected regions. Men are more frequently affected than women, with an approximate ratio of 2.6 : 1. The mean age of onset is 40 years, with almost 80% of patients presenting their first symptoms between 20 and 50 years.[154] If untreated, the disease runs a slowly progressive course[213] with an overall good prognosis, although most patients are impaired in their daily life by reduced dexterity in manual activities.

At present we do not know the cause of MMN. There is substantial, though circumstantial, evidence for an immune-mediated pathogenesis. First, there is the presence of motor nerve conduction block outside nerve compression sites, which is also found in patients with chronic inflammatory demyelinating polyneuropathy (CIDP), second, 20-80% of patients with MMN have increased serum IgM anti-GM1 antibodies. Third, increased signal intensities on T_2-weighted MR images of

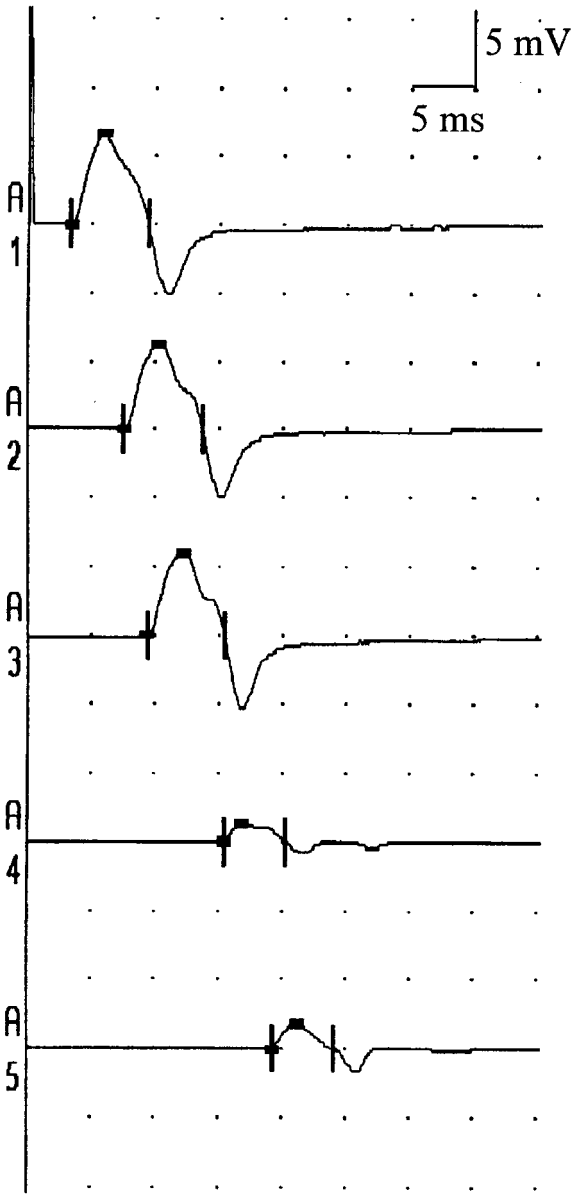

Figure 1. Motor nerve conduction studies in an ulnar nerve, with recording from the m. abductor digiti V and stimulation at the wrist (A1), distal from the elbow (A2), proximal from the elbow (A3), axilla (A4), and Erb´s point (A5), from a patient with multifocal motor neuropathy, showing partial motor conduction block (> 50% reduction of the amplitude and area of the compound muscle action potential) in an upper arm segment (between A3 and A4).

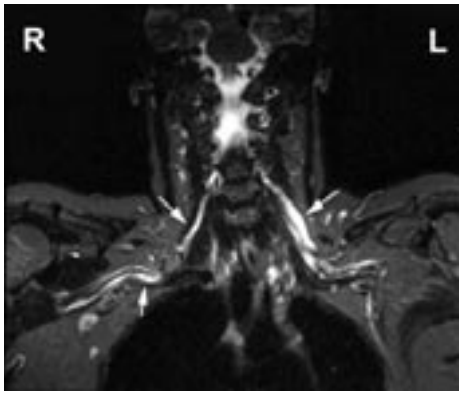

Figure 2. Coronal, fat-suppressed, T2-weigthed, fast-spin echo MRI of the brachial plexus of a patient with multifocal motor neuropathy. Arrows indicate swelling and increased signal intensity. The abnormalities are more pronounced on the -clinically most affected- left than on the right side.

the brachial plexus[237] (figure 2) that have been observed in patients with MMN[237], occur also in patients with CIDP and monoclonal gammopathy of undetermined significance[59], but not in LMND forms.

Finally, various open and placebo-controlled studies have shown that treatment with high-dose IVIg leads to improvement of muscle strength in patients with MMN.[8,62,132,155,226] As the effect of IVIg treatment lasts only several weeks, IVIg maintenance treatment is necessary to maintain the effect on muscle strength in most patients and has been shown to be effective, even over a period of several years.[9,225] Patients who do not respond to immunoglobulins may benefit from cyclophosphamide.[176]

Sporadic lower motor neuron disease with adult onset: classification of subtypes

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Introduction

Amyotrophic lateral sclerosis (ALS) is the most common and most severe form of the motor neuron diseases, eventually leading to death due to respiratory insufficiency within a few years. ALS is characterized by the degeneration of lower motor neurons (LMN) in the anterior horn of the spinal cord or in the brainstem and of upper motor neurons (UMN) in the motor cortex of the brain. In 1994 the El Escorial criteria for ALS were proposed, based on clinical features in four (bulbar, cervical, thoracic and lumbosacral) body regions.[19] To diagnose definite and probable ALS, both UMN and LMN signs have to present in two or more regions. Possible ALS is diagnosed when UMN and LMN signs are found in one region. The diagnosis is less certain in patients with only LMN signs in two or more regions. These patients, who were diagnosed as having suspected ALS according to the 1994 El Escorial criteria and for whom a diagnostic category no longer exists in the 1998 revised El Escorial criteria (**www.wfnals.org**), have progressive muscle atrophy and muscle weakness, but as yet no UMN signs. These patients have been described earlier as having progressive (spinal) muscular atrophy.[6,158] However, patients with only LMN signs but without overt progression have also been described under various names.[72,80,89,102,178] Therefore, the term lower motor neuron disease (LMND) may be used for all diseases in which only LMN signs are found.

In large series of patients with motor neuron disease, approximately 10% have LMN signs only.[25,85,152,157,220] Whether LMND is a distinct nosological entity, separate from ALS, has been debated since Aran first described LMND in 1850.[6] Clinical studies of patients presenting with LMND indicate that a substantial number of patients do develop ALS.[158] In a prospective, population-based study of ALS, 70% of patients with LMN signs had developed UMN and bulbar signs characteristic of ALS after six years.[220] Therefore, probably fewer than 10% of patients with LMND will continue to show LMN signs only. To exclude the majority of patients with ALS, we required a disease duration of more than four years.

Clinical, pathological, and more recently, genetic, electrophysiological, and immunological findings can help to distinguish patients with LMND who never develop ALS from patients with typical ALS. For example, a deletion of the telomeric survival motor neuron (SMN) gene on chromosome 5q13 is found in patients with adult-onset SMN gene-linked spinal muscular atrophy (SMA).[17,33] These patients have symmetrical muscle wasting and weakness of the proximal muscle groups of the limbs and trunk. Spinobulbar muscular atrophy or Kennedy disease is another hereditary form of LMND and is caused by an expansion of CAG trinucleotide repeats in the androgen receptor gene.[113,120] Patients present, usually at

adult age, with slowly progressive, proximal weakness of the limbs associated with facial weakness. The gene defect in other hereditary forms of LMND has not yet been identified.[98,234] Over the last decade, progress has been made in identifying patients with multifocal motor neuropathy (MMN), an immune-mediated lower motor neuron syndrome. Patients with MMN present with a slowly progressive asymmetrical distal weakness of the limbs. Evidence of persistent motor conduction block on electrophysiological examination is considered the electrodiagnostic hallmark of MMN. Importantly, patients with MMN respond to immunological treatment.

These new developments in DNA-proven hereditary LMND and the differentiation of MMN from LMND on the basis of nerve conduction studies, have made some of the earlier reported studies of LMND obsolete. An up-to-date classification of LMND is therefore needed. We describe the clinical and electrophysiological characteristics of 49 patients with sporadic adult onset LMND and define clinical subtypes.

Methods

Study design and patients

The design of this study was cross-sectional. Initially, we reviewed the records of patients in whom a prior diagnosis of LMND, progressive spinal muscular atrophy, focal spinal muscular atrophy or segmental spinal muscular atrophy was made from 1985 to 2000 at the neuromuscular outpatient clinics of the University Medical Centre Utrecht and the Academic Medical Centre of Amsterdam, both tertiary referral centres for MND in the Netherlands. Subsequently, patients were seen for re-appraisal, which consisted of a standardized neurological, laboratory and electrophysiological examination and genetic testing (see below), between 1998 and 2000 by RMvdB-V or JV. Only those patients, who fulfilled the following criteria, were included: (1) age at onset > 18 years, (2) disease duration of > 4 years from the time of onset of weakness, (3) evidence of LMN involvement on neurological examination (weakness, atrophy and fasciculations), and (4) electrophysiological evidence of LMN involvement on needle EMG examination. Exclusion criteria were: (1) familial history of LMND, (2) deletion in the SMN1 gene or an expansion of CAG-repeats (>40) in the androgen receptor gene, (3) history of diseases that may mimic LMND (acute poliomyelitis, spinal radiculopathy, diabetic amyotrophy, thyrotoxicosis or hyperparathyroidism), (4) clinical signs of UMN involvement (pseudobulbar symptoms, clonus of masseter reflex, hyperreflexia (for definition see below) or extensor plantar response), (5) objective sensory signs on neurological examination,

(6) tracheostomy or intermittent ventilatory assistance, (7) structural lesions (tumors, intervertebral disk herniation, vascular lesions, syringomyelia) on magnetic resonance imaging (MRI) or myelography of the spinal cord, and (8) motor conduction block on extensive standardized nerve conduction studies according to previously defined criteria.[231] The following laboratory tests were performed to rule out other diseases: sedimentation rate, hemoglobin, hematocrit, thyroid stimulating hormone, serum immune-electrophoresis with immunofixation, phosphate, calcium (and, if elevated, parathyroid hormone) and serum IgM anti-GM1 antibodies, the latter as described elsewhere.[228]

Clinical evaluation

Muscle strength, muscle atrophy, myotatic reflexes, vital capacity and functional impairment were assessed by RvdB-V or JV. *Muscle strength* was measured by manual muscle testing according to the grading system of the Medical Research Council (MRC)[142], modified to a 9-point scale.[144] Table 1 shows the muscle groups that were measured. Muscle groups were subdivided into upper, middle and lower cervical or lumbosacral regions giving a total of 12 limb regions per patient. Each limb region consisted of two or three myotomes (table 1). For each limb region a mean MRC score was calculated by ascribing the following values to the following MRC grades: MRC 5 = 5.00; MRC 5 - = 4.67; MRC 4+ = 4.33; MRC 4 = 4.00; MRC 4 - = 3.67; MRC 3 = 3.00; MRC 2 = 2.00; MRC 1 = 1.00; MRC 0 = 0.00).[69] We considered a muscle group with a MRC score ≤ 4+ as affected and also calculated the number of affected limb regions. The distribution of weakness was 'symmetrical' if the difference in weakness on the left versus the right side was < 1 on the MRC score in the majority of the affected muscle groups. The presence of *muscle atrophy* was determined in muscle groups and limb regions. Biceps (upper cervical region), triceps (middle cervical region), knee (middle lumbosacral region) and ankle (lower

Table 1 Categorization of muscle groups per limb region

Region	*Muscle groups*	*Myotomes*
Upper cervical region	shoulder abduction, elbow flexion	C5 - C6
Middle cervical region	elbow extension, wrist flexion, wrist extension, extension of fingers	C7 - C8
Lower cervical region	flexion of fingers, spreading of fingers, abduction of thumb, adduction of thumb and opposition of thumb	C8 - Th1
Upper lumbosacral region	hip flexion, hip adduction	L1 - L2
Middle lumbosacral region	hip extension, hip abduction, knee extension, dorsiflexion of foot, extension of toes	L3 - L5
Lower lumbosacral region	knee flexion, plantarflexion of foot, flexion of toes	S1 - S2

lumbosacral region) *reflexes* were scored on both sides according to the NINDS myotatic reflex scale (0 = reflex absent, 1 = reflex small, less than normal, 2 = reflex in lower half of normal range, 3 = reflex in upper half of normal range, 4 = subclonus, 5 = clonus).[76] A reflex score of 4 or 5 was defined as hyperreflexia and was an exclusion criterion. *Respiratory vital capacity* was measured[190] and results are expressed as a percentage of the predicted normal vital capacity. A value > 80% of predicted was considered normal. *Functional impairment* was assessed using the ALS functional rating scale, a 10-item scale that rates the performance of activities of daily living (ADL) and signs and symptoms on a scale from 4 (normal function) to 0 (unable to attempt the task) (maximum 40).[3]

Electrophysiological examination

The distribution of electrophysiological abnormalities was determined by bilateral concentric needle electromyography (EMG) and assessment of compound muscle action potentials (CMAPs). Concentric needle EMG was performed in the m. biceps brachii (upper cervical region), m. flexor carpi radialis (middle cervical region), m. interosseus dorsalis I (lower cervical region) on both sides, in the mm. erectores spinae near Th 6 left and Th 10 right (thoracic region), and in the m. rectus femoris (upper lumbosacral region), m. tibialis anterior (middle lumbosacral region) and m. gastrocnemius caput laterale (lower lumbosacral region) on both sides. A muscle was considered abnormal if there was spontaneous muscle fibre activity (fibrillations, positive sharp waves or complex repetitive discharges) in at least one insertion, or a severely reduced pattern on maximal voluntary effort mainly consisting of long-lasting polyphasic or giant (> 7 mV) motor unit potentials (MUPs) or no insertional and no MUP activity.

CMAPs on stimulation of the most distal site of a nerve were taken from the motor nerve conduction studies that were performed according to a standardized protocol to exclude multifocal motor neuropathy.[231] A CMAP was considered abnormal if the amplitude of the negative peak was below the lower limit of normal (LLN) of our laboratory. We assessed the CMAPs of the m. biceps brachii (LLN 3.0 mV, upper cervical region), m. flexor carpi radialis (LLN 2.9 mV, middle cervical region), m. abductor pollicis brevis (LLN 3.5 mV, lower cervical region) on both sides.

Statistical analysis

Differences in the variables between two groups were tested using the non-parametric Mann-Whitney U test. For a comparison of more than two groups the Kruskal-Wallis test and the Fisher's Exact test for discrete outcome variables were used. A p-value < 0.05 was considered to be statistically significant.

Results

Patients

After reviewing the records of 108 patients, 37 patients were excluded on the basis of a disease duration < 4 years. After re-examination of 71 patients, the diagnosis was changed to MMN in 7 patients, to chronic inflammatory demyelinating polyneuropathy in 2 patients, and to myasthenia gravis, inflammatory myopathy, chronic idiopathic axonal polyneuropathy, idiopathic brachial plexus neuropathy, syringomyelia, myopathy, or herniated lumbar disk in 7 other patients.[241] In one patient the disease duration was unknown. Three patients had upper motor neuron signs and were diagnosed as having ALS. Two patients were excluded because they refused to undergo electrophysiological examination.

The characteristics of the 49 patients who were included in this cross-sectional study are shown in table 2. A male predominance was found. Onset of weakness was most frequently in one distal upper limb. Two female patients first developed bulbar signs, followed by weakness of the arms. At a median disease duration of 12 years,

Table 2. Characteristics of 49 patients

Patient characteristics	
Men / women	39 / 10
Disease duration (median, range)	12 (4 - 37)
Age at onset of weakness (median, range)	41 (18 - 67)
Localization of onset	
limb / bulbar	47 / 2
arms / legs*	32 / 15
distal / proximal*	31 / 16
asymmetrical / symmetrical*	37 / 10
Generalized muscle weakness (> 6 limb regions)	13
symmetrical / asymmetrical	13 / 0
Non-generalized muscle weakness (≤ 6 limb regions)	36
symmetrical / asymmetrical	8 / 28
Disease severity	
Number of affected regions (median, range)	3 (1 - 12)
Mean MRC score / affected region (median, range)	4.2 (2.4 - 4.9)
Number of regions with atrophy (median, range)	3 (1 - 8)
Reflex sumscore (maximum 24) (median, range)	12 (0 - 22)
ALS functional rating scale (maximum 40) (median, range)	37 (26 - 40)
Number of patients with vital capacity < 80%	5
Ancillary investigations	
Positive anti-GM1 antibodies[1]	2
Monoclonal gammopathy	3
Atrophy MRI spinal cord	5
CSF protein g/L (median, range)[2]	0.30 (0.19 - 0.68)
CK U/L (median, range)[3]	173 (46 - 1422)

** = patients with bulbar onset excluded. [1] = investigated in 36 patients. [2] = investigated in 16 patients. [3] = investigated in 37 patients.*

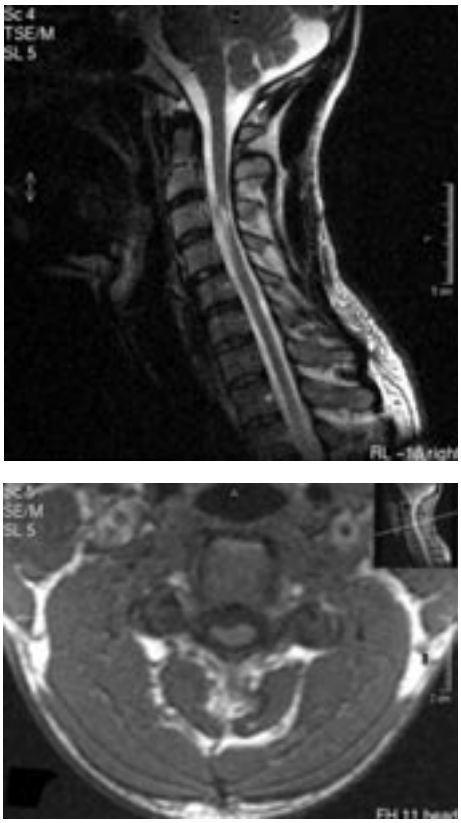


Figure 1. 1.1 Sagittal T2-weighted MRI of the cervical spinal cord with atrophy and increased signal intensity of the cervical spinal cord (C3-C4). 1.2 Transverse T1-weighted MRI at the C3-level, showing atrophy of the spinal cord on the -clinically most affected- right side.

the number of clinically affected limb regions ranged from 1 to 12. In most limb regions weakness was associated with muscle wasting and absent or decreased reflexes, although in a minority of patients also brisk reflexes (score 3 of NINDS reflex scale) were observed at the first affected side. Vital capacity was lower than 80% of predicted in five patients, whose disease durations ranged from 6 to 27 years. Two of these five patients had signs and symptoms of respiratory insufficiency. MRI showed atrophy of the cervical spinal cord in four patients and of the thoracic spinal cord in one patient; in two patients an additional increased signal intensity was seen (figure 1). Two patients had highly elevated titres of IgM anti-GM1 ganglioside antibodies, one with generalized weakness and one with symmetrical distal weakness (see below). The latter patient was one of the four patients who demonstrated atrophy and an increased signal intensity of the cervical spinal cord. Three others had a M-protein: two patients had an IgG lambda monoclonal gammopathy (in one of them the diagnosis of multiple myeloma was made after bone marrow examination), and one patient had both an IgG and IgM lambda monoclonal gammopathy.

Evaluation of subgroups

Patients were subdivided according to the pattern of weakness. Thirteen patients had generalized symmetrical weakness (by definition > 6 affected limb regions) (group 1). Of the 36 patients with non-generalized weakness (≤ 6 affected regions), 8 patients showed symmetrical weakness (group 2) and 28 patients asymmetrical weakness (group 3) (table 2). In group 3, 14 patients had more pronounced weakness in the distal (lower cervical or lumbosacral) limb region (group 3a) and 14

patients had more pronounced weakness in the proximal (upper cervical or lumbosacral) limb region (group 3b).
Disease duration did not differ between the groups (table 3). Age at onset was significantly higher in group 1 than in the other groups (Mann-Whitney U test, $p<0.01$). The onset of weakness was predominantly distal in the legs in group 1 and 2, and in the arms in groups 3a and 3b. At neurological examination, weakness was symmetrical in groups 1 and 2, and asymmetrical in group 3a and 3b. The patients of group 1 had more severe weakness as the mean MRC score per affected region was significantly lower. The patients of group 1 also had muscle atrophy in more limb regions and lower ALS functional rating scale scores. A bulbar onset of symptoms and signs, a vital capacity of < 80% and a M-protein were observed in two, five and three patients of group 1, but not in any patients of the other groups.

Segmental distribution of weakness

To determine whether specific spinal cord segments were preferentially affected, the percentage of patients with affected muscle groups for each limb region was calculated (table 4) and the reflexes were assessed. In patients of group 1, weakness and decreased reflexes were found more frequently and were more severe in the legs than in the arms. In addition, weakness was more severe in the lower cervical and lower lumbosacral regions than in the upper and middle cervical and lumbosacral regions. Reflexes were diffusely decreased in the majority of patients, also more pronounced in the arms than in the legs. In patients of group 2, weakness and decreased reflexes were found predominantly in the lower cervical and lumbosacral regions. In 3 of these patients both arms and legs were affected, with more pronounced weakness in the legs. In 4 patients only the legs and in 1 patient only the arms were affected. Of the patients in group 3a, the lower cervical region was most severely affected in 13 patients and the lower lumbosacral region in 1 patient. In the latter patient, no progression to other limb regions was seen after a disease duration of 22 years. Of the patients with onset in the arms, weakness had progressed over time, such that the middle and upper cervical regions were affected at inclusion in the first affected (ipsilateral) arm in 71% and 21% of patients (table 4), the upper, middle and lower cervical regions were affected in the last affected (contralateral) arm in 14%, 14% and 29% of patients (not shown), and the upper lumbosacral region was affected in 1 patient. This indicates that in the patients in group 3a muscle weakness appeared to spread to adjacent spinal cord segments in a segmental pattern. The reflexes were in the normal range, besides the upper cervical region on the first affected side, in which reflexes were brisk (score 3 of NINDS reflex scale) in half of the patients. Of the patients in group 3b the upper cervical region was most severely affected in 13 patients and the upper lumbosacral region in 1 patient.

Table 3. Disease variables of LMND groups

	Group 1 (N = 13) >6 affected regions symmetrical	*Group 2 (N = 8) ≤ 6 affected regions symmetrical*	*Group 3a (N = 14) ≤ 6 affected regions asymmetrical, distal*	*Group 3b (N = 14) ≤ 6 affected regions asymmetrical, proximal*	*p***
Patient characteristics					
Men / women	10 / 3	7 / 1	9 / 5	13 / 1	0.27
Disease duration (years) (median, range)	11 (6 -27)	14 (4 - 30)	16 (4 - 27)	13 (6 -37)	0.90
Age at onset (years) (median, range)	58 (24 - 67)	33 (18 - 58)	36 (18 - 65)	34 (18 - 62)	0.06
Localization of onset					
limb / bulbar	11 / 2	8 / 0	14 / 0	14 / 0	0.12
arm / leg*	3 / 8	3 / 5	13 / 1	13 / 1	< 0.001
distal / proximal*	9 / 2	8 / 0	14 / 0	0 / 14	< 0.001
asymmetrical / symmetrical*	8 / 3	2 / 6	13 / 1	14 / 0	< 0.001
Disease severity					
No. of affected regions (median, range)	9 (8 - 12)	3 (1 - 6)	2 (1 - 6)	3 (1 - 6)	< 0.001
Mean MRC score / affected region (median, range)	3.9 (2.4 - 4.4)	4.6 (2.7 - 4.7)	4.4 (3.7 - 4.9)	4.1 (2.4 - 4.6)	0.02
No. of regions with atrophy (median, range)	6 (4 - 8)	4 (2 - 4)	2 (1 - 6)	2 (1 - 4)	< 0.001
ALS functional rating scale (median, range)	31 (26 - 38)	38 (31 - 40)	38 (37 - 40)	38 (33 - 40)	< 0.001
Number of patients with vital capacity < 80%	5	0	0	0	0.001
Ancillary investigations					
Positive anti-GM1 antibodies	1	1	0	0	0.22
M-protein	3	0	0	0	0.03
Atrophy MRI spinal cord	2	1	1	1	0.88
CSFprotein g/L (median, range)	0.30 (0.22 - 0.43)	0.47 (0.20 - 0.68)	0.34 (0.25 - 0.39)	0.26 (0.19 - 0.45)	0.51
CK U/L (median, range)	206 (62 - 735)	314 (94 - 1422)	155 (46 - 288)	162 (57 - 335)	0.20

** = 2 patients with bulbar onset excluded. ** = tested using the Kruskal-Wallis test. No. = number.*

Table 4. Segmental distribution of weakness and electrophysiological abnormalities (in percentages of patients affected)

Limb region	*Group 1 (N = 13)*			*Group 2 (N = 8)*		
	Weakness	*CNE*	*CMAPs*	*Weakness*	*CNE*	*CMAPs*
Upper cervical region	69	69	15	13	25	0
Middle cervical region	62	100	8	25	25	13
Lower cervical region	92	85	8	50	63	13
Thoracic region	-	62	-	-	50	-
Upper lumbosacral region	92	85	-	13	88	-
Middle lumbosacral region	92	92	-	38	88	-
Lower lumbosacral region	85	85	-	63	75	-
Limb region	*Group 3a* (N = 14)*			*Group 3b* (N = 14)*		
	Weakness	*CNE*	*CMAPs*	*Weakness*	*CNE*	*CMAPs*
Upper cervical region	21	43	0	100	86	43
Middle cervical region	71	57	0	64	57	7
Lower cervical region	93	93	14	36	43	7
Thoracic region	-	7	-	-	36	-
Upper lumbosacral region	0	29	-	14	7	-
Middle lumbosacral region	0	29	-	7	36	-
Lower lumbosacral region	7	36	-	0	7	-

*CNE = abnormalities at concentric needle EMG. CMAPs = decreased or absent compound muscle action potentials. * = scored on first affected side. - = not available.*

In the latter patient, mild weakness in the upper cervical region on the first affected side was found after a disease duration of 19 years. Of the patients with onset in the arms, the disease had progressed to adjacent spinal cord segments, resulting in weakness at inclusion in the middle and lower cervical regions in the ipsilateral arm in 64% and 36% of patients (table 4) and in the upper, middle and lower cervical region in the contralateral arm in 50%, 21% and 29% of the patients (not shown). The reflexes were in the normal range, besides the biceps reflex (upper cervical region) on the first affected side, which was absent in 6 and decreased in 4 of the 14 patients of group 3b. In all groups the median value of the mean MRC score in the distinct limb regions supported these clinical observations (figure 2). Disease variables did not significantly differ between patients in groups 3a and 3b, except for the male to female ratio, which was 9 : 5 in group 3a and 13 : 1 in group 3b ($p = 0.02$).

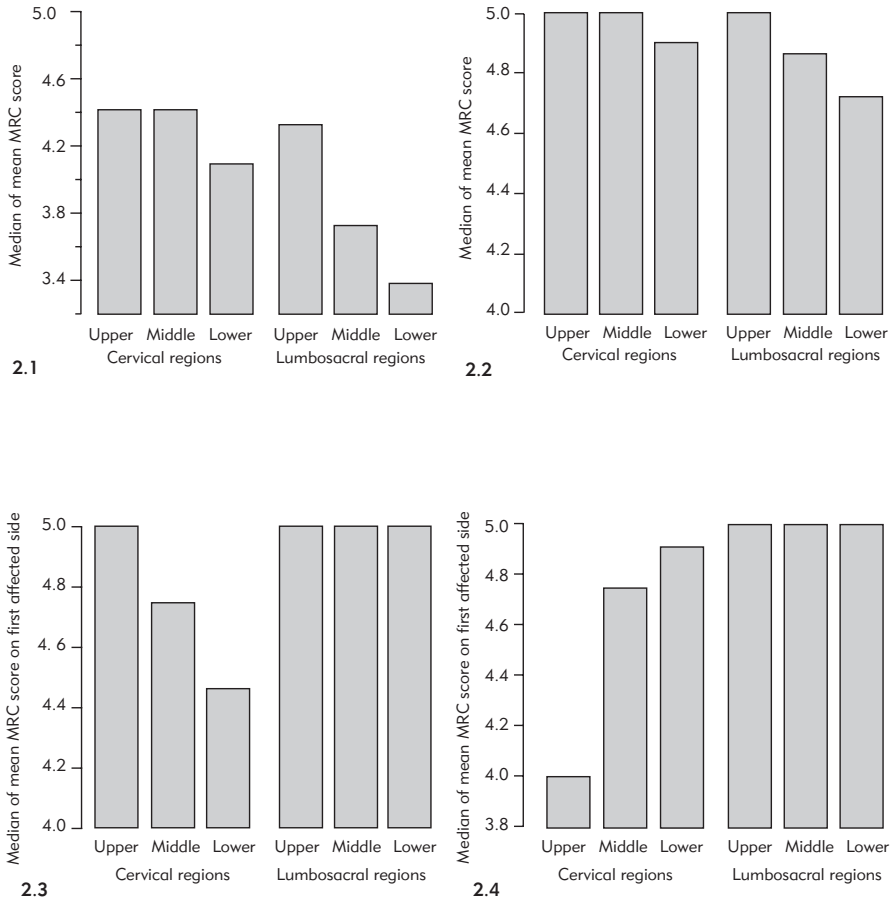


Figure 2. Median values of the mean MRC score in each limb region per group: 2.1 Slowly progressive spinal muscular atrophy. 2.2 Distal spinal muscular atrophy. 2.3 Segmental distal spinal muscular atrophy. 2.4 Segmental proximal spinal muscular atrophy.

Electrophysiological examination

Standardized electrophysiological examination was performed to search for subclinical involvement of the limb regions. Table 4 shows for each limb region the percentage of patients with weakness, abnormalities on concentric needle EMG, and decreased or absent CMAPs. In the majority of limb regions of all groups, more patients had abnormalities on concentric needle EMG in a limb region than had weakness of that region. This was especially true for the upper and middle lum-

bosacral regions of patients in group 2 and for all lumbosacral regions of patients in group 3. In the cervical regions the percentage of patients with abnormalities on concentric needle EMG was compared with the percentage of patients with decreased or absent CMAPs. In all groups more patients had abnormalities on concentric needle EMG than had decreased or absent CMAPs. This can be explained by the fact that due to reinnervation MUPs and CMAPs remain relatively large, while both denervation and reinnervation can be detected by concentric needle EMG.

Case reports

Group 1 (generalized weakness). In 1990, a 56-year-old man developed distal weakness in his left leg, followed by distal weakness in the right leg in 1993. From 1995 onward, the proximal muscles of both legs became weaker, and walking and climbing stairs became impaired. In 2000, the patient noticed diminished strength and dexterity in both hands. One year later, neurological examination showed distal atrophy in the arms and diffuse atrophy in the legs. Weakness of shoulder abductors, elbow flexors, wrist extensors, finger spreaders, thumb abductors and adductors (all MRC 4) on both sides, and weakness of the muscles in both legs (MRC 4 proximally, MRC 4 distally on the right side and MRC 3 on the left side) were found. Reflexes were decreased in the arms and absent in the legs. Vital capacity was normal. Concentric needle EMG revealed widespread denervation and reinnervation in arms, legs and in the thoracic region. Since 1990 the disease course has been gradually progressive.

Group 2 (symmetrical and distal weakness of both arms and legs). In 1982, a 27-year-old woman noticed dragging of both feet while walking and fasciculations in both legs at rest. In 1992 writing became impaired. In 1998 neurological examination showed distal atrophy of both legs. Muscle strength was decreased in finger spreaders, ankle dorsiflexors, ankle plantarflexors, toe flexors and extensors (all MRC grade 4). Reflexes were normal except for absent ankle reflexes on both sides. Vital capacity was normal. Concentric needle EMG revealed signs of denervation and reinnervation in both legs and signs of reinnervation in the right distal arm. Nerve conduction studies showed decreased CMAP-amplitudes in the leg nerves. Since 1982 the disease course has been gradually progressive, but signs and symptoms have remained localized distally in the limbs.

Group 3a (asymmetrical and distal weakness of arms). In 1976 a 30-year-old man slowly developed weakness of his right wrist and finger extensors. He noticed fasciculations and cramps in his right forearm and his writing deteriorated. Surgery to the right radial nerve in 1986 did not lead to improvement. Neurological examination in 1998 showed distal atrophy of the right arm and weakness of the wrist extensors

(MRC grade 3), finger spreaders, finger extensors and thumb abductors and adductors (grade 4). Reflexes were decreased in the right arm. Vital capacity was normal. Concentric needle EMG revealed signs of reinnervation in the right arm distally. Since 1990 signs and symptoms have been stationary.

Group 3b (asymmetrical and proximal weakness of arms). In 1988, a 60-year-old man noticed difficulty with handling cutlery and picking up objects above eye level with his right arm. In 1997 proximal weakness of his left arm developed. He also noticed cramps in both arms. Neurological examination in 1998 revealed atrophy in both shoulder girdles, proximal arms and hands, and fasciculations in the right shoulder girdle. Weakness was found in the shoulder abductors (MRC grade 2 at the right and grade 4 at the left side), elbow flexors and extensors, wrist extensors, finger extensors, finger spreaders and thumb abductors on the right side (all grade 4). Areflexia was observed in all four limbs. Vital capacity was normal. Concentric needle EMG revealed signs of denervation and reinnervation in the proximal arms, in the thoracic region and in one leg distally. Since 1998 proximal weakness in both arms has been progressive, leading to increasing impairments in ADL, such that he has needed assistance in washing and dressing since 2001.

Discussion

We describe the clinical and electrophysiological characteristics of 49 patients with sporadic, adult-onset LMND. In contrast to previous studies, patients were selected on the basis of negative DNA tests and the absence of conduction block or other demyelinating features on extensive nerve conduction studies. Moreover, all patients had a disease duration longer than four years, to exclude the majority of patients with ALS. On the basis of our findings, we propose to classify patients with sporadic adult-onset LMND as follows: slowly progressive spinal muscular atrophy, distal spinal muscular atrophy, segmental distal spinal muscular atrophy and segmental proximal spinal muscular atrophy. The clinical characteristics of these subgroups are discussed in relation to previous studies (reviewed in table 5).

Slowly progressive spinal muscular atrophy (group 1). After a median disease duration of 11 years, these patients had generalized and severe weakness. Five patients had a vital capacity below 80%, but only 2 of them had signs and symptoms of respiratory insufficiency after a disease duration of 11 and 27 years, respectively. It was previously considered that most patients who present with LMN signs would eventually develop ALS, because progression is rapid and UMN signs appear; only patients with slow progression of pure LMN signs should be diagnosed as progressive spinal muscular atrophy.[152,158] To differentiate patients with a slowly progressive disease

course, as included in our study, from patients with a disease course similar to that of ALS, we propose to classify these patients as slowly progressive spinal muscular atrophy. The asymmetrical onset of signs and symptoms found in our patients, and the symmetrical spread of symptoms later in the disease, have been described previously.[78] Our patients with slowly progressive spinal muscular atrophy often showed more severe weakness in the legs than in the arms. Müller also found that weakness in the legs only was much more common in patients with progressive spinal muscular atrophy than in patients with ALS and progressive bulbar palsy.[152] This could not be confirmed in other more heterogeneous groups of patients.[30,78,140] These studies included patients with non-generalized disease forms or patients with MMN, who have more pronounced weakness in the arms.[229] In our study, the age at onset of slowly progressive spinal muscular atrophy was comparable with the age at onset of ALS. Previous studies reported an earlier onset of progressive spinal muscular atrophy[78,152,158], which may be explained by the inclusion of patients with MMN, in whom the disease often starts in the second or third decade. Interestingly, a M-protein was found in three of our patients with slowly progressive spinal muscular atrophy (23%). Although the occurrence of serum M-protein increases with age and the number of patients was small, this could suggest an association between plasma cell dyscrasia and slowly progressive spinal muscular atrophy as has been described previously for both progressive spinal muscular atrophy and ALS.[202]

Distal spinal muscular atrophy (group 2). Sporadic cases with symmetrical and distal muscle weakness in both arms and legs, like the majority of our patients in group 2, have usually been described under the heading of hereditary distal spinal muscular atrophy.[80,138,139,141] However, Harding and Thomas found that of all 78 patients described in the literature, including their own series, only 29 patients showed an autosomal dominant and 8 patients an autosomal recessive inheritance; 41 patients (52%) represented sporadic cases.[80] Although genetically heterogeneous and with an age at onset ranging from 5 to 70 years[197], the clinical presentation of distal spinal muscular atrophy is fairly homogeneous. Slowly progressive symmetrical muscle weakness and atrophy affect the legs and feet first. Years later, the hands and the forearms are affected. Distal spinal muscular atrophy should be differentiated from hereditary motor and sensory neuropathy (HMSN) type 2, the axonal variant of

*Table 5. Year = year of publication. M = male. F = female. Yrs = years. Pts = patients. Progr. = progressive. Dis. course = disease course. Musc. = muscular. * = number of patients with generalized disease forms / total number of patients in the study. ** = number of patients without positive family history / total number of patients in the study. *** = number of patients with arm weakness / total number of patients in the study. Childh. = childhood. Juv. = juvenile. Ipsilat. = ipsilateral. Contralat. = contralateral.*

Table 5. Review of the literature of several forms of LMND, categorized per group

Group	*First author*	*Year*	*No. of patients*	*M : F*	*Age at onset range in yrs*	*Weakness at onset*	*Clinical findings during follow-up*	*Follow-up (yrs)*	*Nomenclature*
1	Swank	1943	26	22 : 4	30 - 70	arm > leg	bulbar symptoms in 5 pts	0.5 - 8	progr. musc. atrophy with fascicular twitchings
	Müller	1952	44	35 : 9	20 - 80	leg > arm	both rapid and slowly progr. dis. course, with and without bulbar symptoms	3 - 30	progr. spinal musc. atrophy
	Meadows	1969	8	6 : 2	18 - 62	arm > leg	slowly progr. dis. course, no bulbar symptoms	7 - 18	chronic progr. musc. atrophy
	Harding	1983	13*/ 18	8 : 5	24 - 47	arm > leg	slowly progr. dis. course, no bulbar symptoms	1 - 23	chronic asymmetrical spinal musc. atrophy
	Chio	1985	78*/ 155	60 : 18	20 - 70	arm > leg	rapid progr. dis. course, 3-yrs survival 40%	2 - 17	progr. musc. atrophy
2	Meadows	1969	3**/ 6	3 : 0	childh. - 45	distal leg > distal arm	unknown	decades	chronic spinal musc. atrophy of distal symmetrical distribution
	McLeod	1971	3**/ 6	3 : 0	5 - 11	distal leg	distal arm weakness in 2 pts	unknown	distal type of chronic spinal musc. atrophy
	Harding	1980	18**/ 34	9 : 9	10 - 20	distal leg	distal arm weakness in 3 pts	unknown	hereditary distal spinal musc. atrophy
3a	Hirayama	1963	20	20 : 0	15 - 20	distal arm	unknown	unknown	juv. musc. atrophy of unilateral upper extremity
	Hashimoto	1976	27	27 : 0	13 - 20	distal arm	contralat. distal arm weakness in 8 pts	0.5 - >5 (15 pts)	juv. nonprogr. musc. atrophy of hand and forearm
	Sobue	1971	71	59 : 12	18 - 22	distal arm	contralat. distal arm weakness in 24 pts, ipsilat. proximal weakness in 10% of pts	3 - 10	juv. type of distal and segmental musc. atrophy of upper extremities
	Singh	1980	24	23 : 1	11 - 26	distal arm	contralat. distal arm weakness in 9 pts, ipsilat. proximal weakness in 2 pts	2 - 9	juv. musc. atrophy localized to arms
	Gourie-Devie	1984	13***/ 23	11 : 2	15 - 32	distal arm	ipsilat. proximal arm weakness in 5 pts	1 - 5	monomelic amyotrophy
	Peiris	1989	102	93 : 9	13 - 29	distal arm	contralat. distal leg weakness in 63 pts, ipsilat. proximal weakness in 5 pts	1 - 14	juv. distal spinal musc. atrophy of upper extremity
	Hirayama	2000	73	68 : 5	11 - 19	distal arm	contralat. distal arm weakness in 13 pts	unknown	juv. musc. atrophy of distal upper extremity
3b	Kaeser	1983	5	5 : 0	15 - 35	proximal arm	ipsilat. distal arm + contralat. proximal arm weakness in 4 pts, leg affected in 1 pt	20 - 40	unilateral scapulohumeral musc. atrophy
	Katz	1999	10	6 : 4	35 - 68	proximal arm	ipsilat. distal arm + contralat. proximal leg weakness in 3 pts, neck affected in 1 pt, leg in 3 pts	0.2 - 7	brachial amyotrophic diplegia
	Total number of pts		538	458 : 80 (6 : 1)					

Charcot-Marie-Tooth disease, in which clinical sensory loss is not always present.[79] Features which distinguish between distal spinal muscular atrophy and HMSN type 2 are more common upper limb weakness[80] and low or absent sensory action potentials in HMSN type 2.[77] In our eight patients the results of the sensory examination were normal, both clinically and electrophysiologically. In group 2 in particular, electrophysiological analysis showed evidence of a more generalized disease pattern, with subclinical involvement of the upper and middle lumbosacral regions.

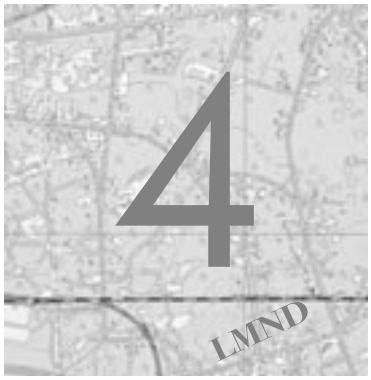
Segmental distal spinal muscular atrophy (group 3a). The clinical presentation of muscular atrophy and weakness in the hand and forearm of the patients of group 3a was first described by Hirayama[89], who proposed the term juvenile muscular atrophy of *uni*lateral upper extremity. Later, he replaced unilateral by distal, when about 33% of patients were found to have less pronounced contralateral weakness of the hand and forearm.[82,86] Both Hirayama and Sobue reported that the deltoid, biceps and triceps brachii muscles could be affected and that reflexes could be brisk in the affected arm.[89,206] Proximal weakness in the ipsilateral arm and distal weakness in the contralateral arm, together with brisk reflexes, were also found in 21% and 29% of our patients, who were all caucasian, in contrast with those described by Hirayama. This demonstrates that the disease progresses to adjacent spinal cord segments, and therefore we suggest the term segmental distal spinal muscular atrophy. In addition, abnormalities on concentric needle EMG were found in lower limb regions in about 33% of patients, suggesting an even more widespread disease of the spinal cord. In one of our patients, atrophy and an increased signal intensity of the cervical spinal cord at the level C3-C4 were found, which may represent focal corticospinal tract damage of unknown pathogenesis, and has also been described by others.[156] We found an older age at onset and a higher proportion of women to be affected than in other studies. Nevertheless, these patients appeared to have a relatively benign disease form as symptoms and signs were still confined to two limb regions after a median disease duration of 16 years. The notion that Hirayama disease could also occur in women and older patients is important for clinical practice.

Segmental proximal spinal muscular atrophy (group 3b). The phenotype of asymmetrical proximal weakness in the arms in the patients of group 3b is less well known. Both Kaeser and Katz previously described patients with ipsilateral muscle weakness and wasting in shoulder and proximal arm muscles[102,110], which after years progressed to the contralateral shoulder in a majority, and to the lower limb and neck muscles in a minority of patients. A similar mode of disease progression with involvement of adjacent spinal cord segments was found in the majority of our patients. In one patient mild leg weakness developed after a disease duration of more than 20 years. These findings not only suggest widespread involvement of the cervical anterior horn cells, but also of motor neurons in the thoracic and lumbosacral regions.

Concentric needle EMG revealed abnormalities in thoracic and leg muscles. The proximal weakness measured in the first affected arm was often relatively severe and comparable with that seen in the patients with slowly progressive spinal muscular atrophy (table 3) and resulted in a man-in-the-barrel phenotype[91,110] in two of our patients. The striking male predominance that we found is comparable with that described by Kaeser (table 5).[102] In addition, Hu et al. also found a male: female ratio of 9 : 1 in the subgroup of ALS patients with a man-in-the-barrel phenotype.[91] Although this form of LMND appears to carry a favourable prognosis, as Kaeser already stated, it nevertheless may cause considerable functional impairment in ADL. One patient in each of the subgroups 3a and 3b demonstrated weakness in one leg only, and the weakness remained localized to this leg for years. These patients could also be categorised under the heading of monomelic amyotrophy of lower limb, a disease form that is most often reported in India.[72,178]

In the different types of LMND described in this study, most of the affected patients were male. The male to female ratio of 4 : 1 in our study is comparable with the ratio of 6 : 1 described in the literature (table 5). This suggests that not yet identified genetic or hormonal factors play a role in the pathogenesis. Importantly, after a disease duration with a median of 12 years for the whole group, the majority of patients of group 1 with the generalized disease form still had no respiratory symptoms and the patients of groups 2 and 3 with non-generalized disease forms were still relatively mildly affected without respiratory insufficiency. Retrospectively, the prognosis of sporadic LMND with adult onset thus seems to be relatively good. The clinical phenotypes of the different subgroups described in this study may help to differentiate the several LMND forms from each other. However, at present it is not known how long patients have to be observed before the diagnosis LMND can be made with certainty. Prospective studies are needed to investigate whether specific clinical or pathogenic variables may help to identify patients with a more benign form of LMND.

A prospective study of the natural course of sporadic adult-onset lower motor neuron disease



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In preparation

Introduction

The term lower motor neuron disease (LMND) is used to denote a group of disease forms with a clinical presentation of lower motor neuron (LMN) signs, i.e. weakness, atrophy and fasciculations, in the voluntary muscles of the limbs and bulbar regions. This disease entity is not well-defined and is relatively rare. In large series of patients with motor neuron disease, approximately 10% of patients have LMN signs only.[25,85,152,157,220] Whether LMND is a distinct nosological entity, separate from ALS, has been debated since Aran first described LMND in 1850.[6] Clinical studies of patients presenting with LMND indicate that a substantial number of patients develop clinical signs of upper motor neuron (UMN) degeneration[220], show a disease progression that is as rapid as in amyotrophic lateral sclerosis (ALS) or show UMN pathology at autopsy.[20,124] One might argue that these patients suffer from ALS, rather than from LMND.

In the remainder of patients with LMND, several clinical phenotypes have been described. Recently, we have classified these patients according to the pattern of muscle weakness at disease onset, resulting in the following subtypes: 'slowly progressive spinal muscular atrophy' with generalized weakness, 'distal spinal muscular atrophy' with symmetrical, distal weakness more in the legs than in the arms, 'segmental distal spinal muscular atrophy' and 'segmental proximal spinal muscular atrophy' with asymmetrical weakness predominantly distal, respectively proximal in the arms *(see chapter 3)*. The prognosis of these LMND forms appeared to be favourable, because after a median disease duration of 14 years, the majority of patients with generalized weakness still had no respiratory symptoms and in most patients with non-generalized weakness clinical abnormalities were confined to the limb(s) in which weakness had started. However, the natural disease course of LMND is not known. We prospectively measured muscle strength, respiratory function and functional impairment in patients with sporadic adult-onset LMND forms to determine the course of the disease. A disease duration of more than four years was chosen to exclude patients with ALS.

Methods

Patients

In 1998 the Academic Medical Centre (AMC) in Amsterdam and the University Medical Centre in Utrecht (UMCU) started a joint prospective study of LMND. Patients in whom a prior diagnosis of LMND had been made, were asked to participate. All these patients had been diagnosed by experienced neurologists. Selection

took place by screening of the files of our outpatient neuromuscular departments for the following diagnoses: LMND, progressive spinal muscular atrophy, focal spinal muscular atrophy and segmental spinal muscular atrophy. In addition, newly diagnosed patients at the outpatient clinics of the tertiary referral centres at the AMC and UMCU were asked to enter into the study. Six patients were recruited from other university hospitals. We included three members of the Dutch Neuromuscular Diseases Association with a diagnosis of progressive spinal muscular atrophy, who referred themselves for participation.

All patients underwent re-appraisal before inclusion in this prospective study. Inclusion criteria were: (1) age at onset > 18 years, (2) disease duration of > 4 years from the time of onset of weakness, (3) evidence of LMN involvement on neurological examination (weakness, atrophy and fasciculations), and (4) electrophysiological evidence of LMN involvement on needle EMG examination. Exclusion criteria were: (1) familial history of LMND, (2) deletion in the SMN1 gene or an expansion of CAG-repeats (>40) in the androgen receptor gene, (3) history of diseases that may mimic LMND (acute poliomyelitis, spinal radiculopathy, diabetic amyotrophy, thyreotoxicosis or hyperparathyroidism), (4) clinical signs of UMN involvement (pseudobulbar symptoms, clonus of masseter reflex, hyperreflexia (for definition see below) or extensor plantar response), (5) objective sensory signs on neurological examination, (6) tracheostomy or intermittent ventilatory assistance, (7) structural lesions (tumors, intervertebral disk herniation, vascular lesions, syringomyelia) on magnetic resonance imaging (MRI) or myelography of the spinal cord, and (8) motor conduction block on extensive standardized nerve conduction studies according to previously defined criteria.[231] The following laboratory tests were performed to rule out other diseases: sedimentation rate, hemoglobin, hematocrit, thyroid stimulating hormone, serum immunelectrophoresis with immunofixation, phosphate, calcium (and, if elevated, parathyroid hormone) and serum IgM anti-GM1 antibodies, the latter as described elsewhere.[228] Patients who were no longer able to visit the outpatient clinic due to advanced functional impairment were followed-up by telephone. For patients lost to follow-up, the reasons for withdrawal were noted. The study was approved by the medical ethics committee of the AMC and UMCU and written informed consent was obtained from all participants.

Clinical evaluation

Patients were seen at inclusion and, assuming that the disease course was progressing slowly over years or even stationary, subsequently at month six, twelve and eighteen. At each visit, the following measurements were assessed by the same investigator (RvdB-V or JV) in each patient: muscle strength, muscle atrophy, reflexes, respiratory function and functional impairment. Muscle strength was measured by

manual muscle testing according to the grading system of the Medical Research Council (MRC)[142], modified to a 9-point scale.[144] Table 1 shows the muscle groups that were measured. Muscle groups were subdivided into upper, middle and lower cervical or lumbosacral regions giving a total of 12 limb regions per patient. Each

Table 1. Categorization of muscle groups per limb region

Region	*Muscle groups*	*Myotomes*
Upper cervical region	shoulder abduction, elbow flexion	C5 - C6
Middle cervical region	elbow extension, wrist flexion, wrist extension, extension of fingers	C7 - C8
Lower cervical region	flexion of fingers, spreading of fingers, abduction of thumb, adduction of thumb and opposition of thumb	C8 - Th1
Upper lumbosacral region	hip flexion, hip adduction	L1 - L2
Middle lumbosacral region	hip extension, hip abduction, knee extension, dorsiflexion of foot, extension of toes	L3 - L5
Lower lumbosacral region	knee flexion, plantarflexion of foot, flexion of toes	S1 - S2

limb region consisted of two or three myotomes (table 1). For each patient a mean MRC score per limb region was calculated by ascribing the following values to the following MRC grades: MRC 5 = 5.00; MRC 5 - = 4.67; MRC 4+ = 4.33; MRC 4 = 4.00; MRC 4 - = 3.67; MRC 3 = 3.00; MRC 2 = 2.00; MRC 1 = 1.00; MRC 0 = 0.00.[69] We considered a muscle group with a MRC score ≤ 4+ as affected and calculated the number of affected limb regions. The distribution of weakness was 'symmetrical' if the difference in weakness on the left versus the right side was < 1 on the MRC score in the majority of the affected muscle groups. The presence of muscle atrophy was determined in muscle groups and limb regions. Muscle tone was assessed using the modified Ashworth scale.[13] The biceps, triceps, knee and ankle reflexes and the masseter reflex and plantar response were scored on both sides according to the NINDS myotatic reflex scale (0 = reflex absent, 1 = reflex small, less than normal, 2 = reflex in lower half of normal range, 3 = reflex in upper half of normal range, 4 = subclonus, 5 = clonus).[76] A reflex score of 4 or 5 was defined as hyperreflexia and was an exclusion criterion. A NINDS reflex sum-score was calculated (maximum 24). Respiratory function was assessed by measuring slow vital capacity (sVC).[190] Results are expressed as a percentage of the predicted normal vital capacity. A value > 80% of predicted was considered normal. Functional impairment was assessed using an ALS functional rating scale that rates the performance of activities of daily living (ADL) and signs and symptoms on a scale from 4 (normal function) to 0 (unable to attempt the task) (maximum 40).[3] The ALS functional ra-

ting scale consists of a 10-item scale, divided in the following subscales: 3 items for bulbar muscles, 3 items for arm functioning, 1 item for truncal muscles, 2 items for leg functioning and 1 item for breathing.

Statistical analyses

To estimate the rate of decline for the muscle strength, the number of affected limb regions, the percentage of sVC, and the ALS functional rating scale, we used a random effects model for repeated measurements (SAS version 8, PROC MIXED). We assumed a linear rate of decline. All baseline and follow-up measurements were taken as outcome variables and the intercept and time variables were specified as random effects to allow for individual differences. To test for differences in the slopes of the outcome variables between the diagnostic subgroups, the variables subgroup, follow-up time, and an interaction term of subgroup with time were entered as covariates in the random effects model.

Results

Patients

Of the 89 patients who were considered for inclusion in the present study, 37 patients were excluded on the basis of a disease duration less than four years. After re-appraisal in 17 patients another diagnosis than LMND was made, of whom we reported separately *(see chapter 6)*. Thirty-five patients with a disease duration over four years were included in the present study.

The 35 patients were subdivided according to the pattern of weakness as described previously (*see chapter 3*), resulting in the following groups: 9 patients with generalized (> 6 affected limb regions) weakness (slowly progressive spinal muscular atrophy, group 1), 6 patients with distal, symmetrical weakness more in the legs than in the arms (distal spinal muscular atrophy, group 2) and 20 patients with segmental weakness of the arms (group 3). In group 3, 6 patients had predominantly distal weakness (group 3a, segmental distal spinal muscular atrophy) and 14 patients had predominantly proximal weakness (group 3b, segmental proximal spinal muscular atrophy). The baseline characteristics are shown in table 2.

Muscle strength

Muscle strength declined significantly and the number of affected limb regions increased significantly in the whole group of patients (table 3). For the patients with slowly progressive spinal muscular atrophy the decline of muscle strength and the increase of affected limb regions were significant (figure 1.1, 1.2). The decline in

Table 2 Disease variables of four LMND groups at baseline

Patient characteristics	*Slowly PSMA (1)* *n = 9*	*Distal SMA (2)* *n = 6*	*Segmental distal SMA (3a)* *n = 6*	*Segmental proximal SMA (3b)* *n = 14*
Male / female patients	6 / 3	5 / 1	4 / 2	13 / 1
Disease duration (years) (median, range)	14 (6 -27)	18 (10 - 30)	13 (10 - 27)	13 (6 - 37)
Age at onset (years) (median, range)	57 (18 - 67)	32 (18 - 49)	43 (29 - 65)	34 (18 - 62)
Localization of onset				
limb / bulbar	8 / 1	6 / 0	6 / 0	14 / 0
upper limb / lower limb*	3 / 5	2 / 4	6 / 0	13 / 1
distal / proximal*	7 / 1	6 / 0	6 / 0	0 / 14
asymmetrical / symmetrical*	6 / 2	2 / 4	6 / 0	14 / 0
Disease severity				
Mean MRC score / limb region (median, range)	4.1 (2.8 - 4.7)	4.8 (3.4 - 5.0)	4.9 (4.7 - 5.0)	4.8 (3.8 - 5.0)
Number of affected limb regions (median, range)	8 (7 - 12)	5 (1 - 6)	2 (1 - 4)	3 (1 - 6)
Number of limb regions with atrophy (median, range)	6 (4 - 8)	4 (2 - 4)	1 (1 - 2)	2 (1 - 4)
Reflex sumscore (median, range)	11 (0 - 20)	12 (4 - 22)	12 (6 - 16)	10 (0 - 20)
Number of patients with sVC < 80%	3	0	0	0
ALS functional rating scale (median, range)	31 (27 - 38)	38 (31 - 40)	38 (37 - 40)	38 (33 - 40)
Ancillary investigations				
Positive anti-GM1 antibodies	0	1	0	0
Monoclonal gammopathy	2	0	0	0
Atrophy MR imaging spinal cord	1	1	0	1
CSFprotein g/L (median, range)	0.30 (0.22 - 0.43)	0.47 (0.20 - 0.68)	0.39**	0.26 (0-19 - 0.45)
CK U/L (median, range)	179 (62 - 735)	161 (94 - 1422)	139 (66 - 288)	162 (57 - 335)

*PSMA = progressive spinal muscular atrophy. SMA = spinal muscular atrophy. * = 1 patient with bulbar onset excluded. sVC = slow vital capacity. ** = only performed in 1 patient of this group.*

Table 3. Slopes of variables and differences between subgroups

Limb region	*All patients (n = 35)*		*Slowly PSMA (n = 9)*		*Distal SMA (n = 6)*	
	Slope (β)	*p*	*Slope (β)*	*p*	*Slope (β)*	*p*
Mean MRC score / limb region	- 0.03	0.001	- 0.08	0.02	- 0.01	0.57
Number of affected limb regions	0.25	0.007	0.44	0.01	0.05	0.89
ALS functional rating scale	- 0.42	0.0002	- 0.89	0.02	- 0.42	0.06
Percentage of sVC	- 0.17	0.78	- 0.98	0.54	1.38	0.46

Limb region	*Segmental distal SMA (n = 6)*		*Segmental proximal SMA (n =14)*		*Segmental distal + proximal SMA (n = 20)*	
	Slope (β)	*p*	*Slope (β)*	*p*	*Slope (β)*	*p*
Mean MRC score / limb region	- 0.02	0.11	- 0.02 *	0.04	- 0.02	0.008
Number of affected limb regions	0.33	0.14	0.18	0.13	0.23	0.03
ALS functional rating scale	- 0.12 *	0.36	- 0.25 *	0.01	- 0.21	0.008
Percentage of sVC	0.77	0.62	- 0.71	0.30	- 0.27	0.67

*β = coefficient of plotted line. PSMA = progressive spinal muscular atrophy. SMA = spinal muscular atrophy. * = significant difference from slope of group 1. sVC = slow vital capacity.*

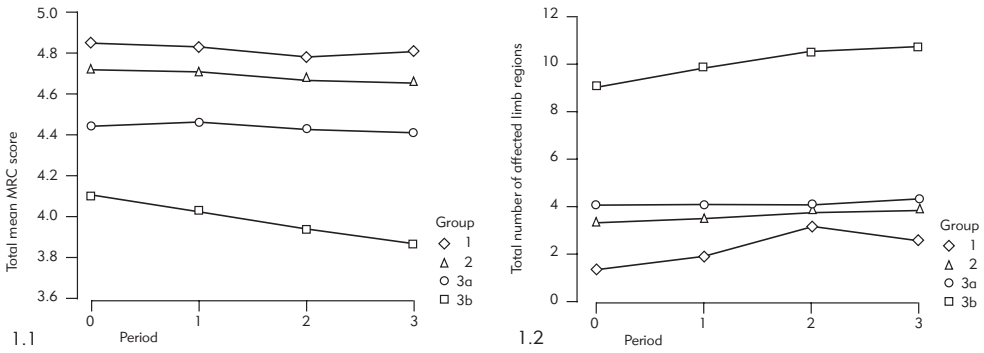

Figure 1. Disease variables during follow-up per group: 1 = slowly progressive spinal muscular atrophy, 2 = distal spinal muscular atrophy, 3a = segmental distal spinal muscular atrophy, 3b = segmental proximal spinal muscular atrophy. 1.1 Muscle strength. 1.2 Number of affected limb regions.

muscle strength was most pronounced in two patients who also developed respiratory insufficiency (see below). The increase of affected limb regions occurred uniformely distributed over all patients with slowly progressive spinal muscular atrophy. In the other groups the decline of the muscle strength and the increase of the number of affected limb regions were not significant (table 3). One patient with segmental distal SMA and one patient with segmental proximal SMA developed more generalized and more severe muscle weakness during follow-up than the other patients of those groups. These two patients had a disease duration of 22 and 28 years. The small increase of the number of affected limb regions that was found during follow-up in the remaining patients of these groups occurred uniformely distributed over all patients.

Distribution of weakness

In our previous study we found that in patients with slowly progressive spinal muscular atrophy the legs were more severely affected than the arms and distal limb regions were more severely affected than proximal ones (*see chapter 3*). This remained so during follow-up (figure 2.1, table 4). Nevertheless, during follow-up a decline of muscle strength was also seen in the arms. In the patients with distal SMA a predilection of weakness in the legs more than in the arms was also found at baseline (figure 2.2, table 4). Muscle weakness was most pronounced in the lower cervical region and relatively less pronounced in the lower lumbosacral region (figure 2.2). In the former limb region five muscle groups of the hands are included whereas in the latter limb region two muscle groups in the feet are included and the mus-

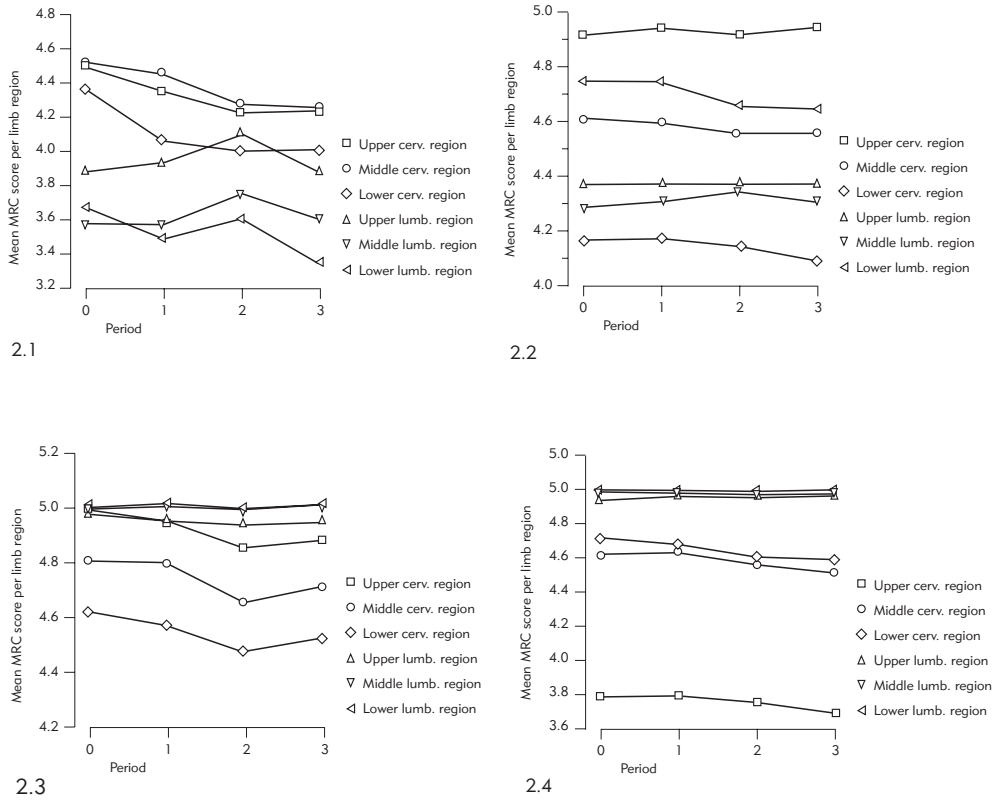

Figure 2. Muscle strength per limb region during follow-up per group: 2.1 Slowly progressive spinal muscular atrophy. 2.2 Distal spinal muscular atrophy. 2.3 Segmental distal spinal muscular atrophy. 2.4 Segmental proximal spinal muscular atrophy.

cle group knee flexion, which was affected less severely. During follow-up the distribution of weakness in the patients with distal SMA remained the same (figure 2.2, table 4). The distribution of muscle weakness in the patients with segmental distal SMA and segmental proximal SMA also remained the same during follow-up (figure 2.3 and 2.4, table 4). At the last measurement, we found that muscle weakness had spreaded to adjacent spinal cord segments in a segmental pattern compared with at baseline, as a mild decrease of muscle strength was found in the upper cervical region at the first affected side for the patients with segmental distal SMA and in the lower cervical region at the first affected side for the patients with segmental proximal SMA (table 4).

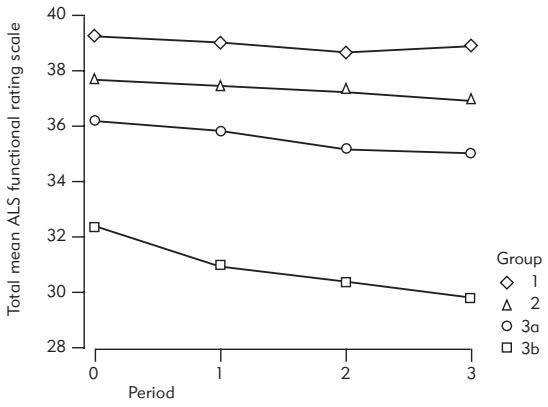

Figure 3. Functional impairment during follow-up per group: 1 = slowly progressive spinal muscular atrophy, 2 = distal spinal muscular atrophy, 3a = segmental distal spinal muscular atrophy, 3b = segmental proximal spinal muscular atrophy.

Functional impairment

Functional impairment increased significantly during follow-up in the whole group of patients (table 3). The decline of the ALS functional rating scale could be attributed to the three items that assessed arm functioning, because only this subscale declined significantly during follow-up (not shown). The increase of functional impairment was most pronounced in the patients with slowly progressive spinal muscular atrophy (figure 3).

Respiratory function

The percentages of sVC did not significantly decrease in the whole group of patients (table 3). In two of the nine patients with slowly progressive spinal muscular atrophy signs and symptoms of respiratory insufficiency were present at inclusion with percentages of 38% and 70% of predicted. These progressed during follow-up and led to the installment of intermittent (nocturnal) ventilatory assistance in the former patient during and in the latter patient six months after the end of the study. Shortness of breath with minimal exertion developed in one patient during the study and in one patient shortly after the study. This led to death due to a sudden, suspected cardiac cause and respiratory failure, respectively 11 and 15 months after the end of the study, after a disease duration of 13 and 9 years.

UMN signs

The patient with slowly progressive spinal muscular atrophy who died suddenly 11 months after the end of the study, was the only patient with a bulbar onset of symp-

Table 4. Segmental distribution of weakness

Limb region	*Slowly PSMA (N = 9)*				*SMA (N = 6) Distal*			
	MRC score[1]		*% of patients affected*[2]		*MRC score*[1]		*% of patients affected*[2]	
	t = 0	*t = 3*	*t = 0*	*t = 3*	*t = 0*	*t = 3*	*t = 0*	*t = 3*
Upper cervical region	4.7 (3.4 - 5.0)	4.3 (3.0 - 5.0)	67	89	5.0 (4.5 - 5.0)	5.0 (4.8 - 5.0)	17	17
Middle cervical region	4.5 (3.8 - 5.0)	4.3 (3.5 - 5.0)	67	89	5.0 (2.8 - 5.0)	5.0 (2.5 - 5.0)	17	33
Lower cervical region	4.4 (3.5 - 5.0)	3.8 (3.1 - 4.8)	78	100	4.9 (0.8 - 5.0)	4.9 (0.1 - 5.0)	50	50
Upper lumbosacral region	4.3 (1.0 - 5.0)	4.5 (1.3 - 4.8)	78	89	5.0 (1.3 - 5.0)	5.0 (1.3 - 5.0)	17	17
Middle lumbosacral region	3.7 (1.3 - 5.0)	3.7 (1.2 - 5.0)	78	89	4.7 (2.2 - 4.9)	4.8 (1.7 - 5.0)	50	67
Lower lumbosacral region	3.6 (1.7 - 5.0)	3.3 (1.0 - 5.0)	67	89	4.7 (4.5 - 5.0)	4.7 (3.8 - 5.0)	67	50
Limb region	*Segmental distal SMA* (N = 6)*				*Segmental distal SMA** (N = 6)*			
	MRC score[1]		*% of patients affected*[2]		*MRC score*[1]		*% of patients affected*[2]	
	t = 0	*t = 3*	*t = 0*	*t = 3*	*t = 0*	*t = 3*	*t = 0*	*t = 3*
Upper cervical region	5.0 (3.8 - 5.0)	4.8 (4.5 - 5.0)	0	17	5.0 (4.7 - 5.0)	5.0 (4.7 - 5.0)	0	17
Middle cervical region	4.7 (3.7 - 5.0)	4.7 (3.1 - 5.0)	50	67	5.0 (4.7 - 5.0)	5.0 (4.9 - 5.0)	0	0
Lower cervical region	4.2 (3.3 - 5.0)	4.4 (2.8 - 4.9)	100	100	5.0 (4.6 - 5.0)	5.0 (4.7 - 5.0)	0	33
Upper lumbosacral region	5.0 (4.8 - 5.0)	5.0 (4.7 - 5.0)	0	17	5.0 (4.7 - 5.0)	5.0 (4.7 - 5.0)	0	17
Middle lumbosacral region	5.0 (4.9 - 5.0)	5.0	0	0	5.0	5.0	0	0
Lower lumbosacral region	5.0 (4.7 - 5.0)	5.0	0	0	5.0	5.0	0	0
Limb region	*Segmental proximal SMA* (N = 14)*				*Segmental proximal SMA** (N = 14)*			
	MRC score[1]		*% of patients affected*[2]		*MRC score*[1]		*% of patients affected*[2]	
	t = 0	*t = 3*	*t = 0*	*t = 3*	*t = 0*	*t = 3*	*t = 0*	*t = 3*
Upper cervical region	3.9 (0.0 - 4.5)	4.0 (0.0 - 4.7)	100	100	4.7 (1.5 - 5.0)	4.6 (1.0 - 5.0)	50	71
Middle cervical region	4.8 (2.5 - 5.0)	4.7 (1.8 - 5.0)	57	71	5.0 (2.7 - 5.0)	5.0 (2.7 - 5.0)	29	29
Lower cervical region	5.0 (2.3 - 5.0)	4.8 (1.8 - 5.0)	29	50	5.0 (3.0 - 5.0)	5.0 (2.7 - 5.0)	29	36
Upper lumbosacral region	5.0 (4.7 - 5.0)	5.0 (4.5 - 5.0)	21	14	5.0 (4.7 - 5.0)	5.0 (4.7 - 5.0)	7	14
Middle lumbosacral region	5.0 (4.6 - 5.0)	5.0 (4.5 - 5.0)	7	7	5.0	5.0 (4.9 - 5.0)	0	7
Lower lumbosacral region	5.0 (4.8 - 5.0)	5.0 (4.8 - 5.0)	7	7	5.0	5.0 (4.9 - 5.0)	0	7

*PSMA = progressive spinal muscular atrophy. SMA = spinal muscular atrophy. 1 = median (range) of sum score. 2 = the number of affected limb regions was calculated from the muscle groups with a MRC score ≤ 4+. % = percentage. * = scored on first affected side. ** = scored on last affected side.*

toms and signs. During follow-up she developed hyperreflexia in the legs, while plantar responses remained flexor. One patient with segmental proximal SMA had developed hyperreflexia in the limbs at the last visit and the diagnosis ALS was made. A sister of the patient with slowly progressive spinal muscular atrophy who received intermittent (nocturnal) ventilatory assistance after the end of the study, developed bulbar ALS, and the diagnosis in this patient was changed in familial ALS. In the remainder of the patients no UMN signs developed during follow-up. Hypertonia of the limbs was not found during follow-up.

Discussion

In the group of LMND patients as a whole, we prospectively found a significant decline of muscle strength and a significant increase of functional impairment and 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 progressive spinal muscular atrophy, but were also significant for patients with segmental 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 UMN signs developed and the diagnosis was changed into 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.
So far only one retrospective[195] and two prospective studies[30,152] of the natural course of LMND have been published. These studies demonstrated methodological shortcomings. First, it concerned heterogeneous groups of patients in whom the several clinical phenotypes of LMND were not differentiated well and second, the assessment of muscle strength, respiratory function and UMN signs was not performed repeatedly. In these two prospective studies, the 3-year survival rate for patients with generalized LMN signs was 43%.[152] As most patients that died had developed bulbar involvement or UMN signs[152], and thus also may have suffered from ALS, the survival rate of patients who will continue to show LMN signs only will be higher. Although the design of our study was inappropriate to calculate survival rates, we found evidence that patients with slowly progressive spinal muscular atrophy suffer from a relatively severe form of MND. Weakness was severe and generalized, functional impairment was considerable and respiratory insufficiency was present during or shortly after the study in four of the nine patients. In one of these patients, who had a bulbar onset of symptoms and signs, UMN signs devel-

oped so she most likely has suffered from ALS. In another patient, who received intermittent (nocturnal) ventilatory assistance, the diagnosis familial ALS was made. It could therefore be postulated that slowly progressive spinal muscular atrophy overlaps with ALS. As a consequence, patients with slowly progressive spinal muscular atrophy could also benefit from treatment with the glutamate-inhibitor riluzole, the only drug of which a significant therapeutic effect in ALS has been demonstrated.[122] Because slowly progressive spinal muscular atrophy is rare and disease progression is slow compared with that of ALS, a double-blind placebo-controlled study on the effect of riluzole will be difficult to realize and thus the decision whether patients should be treated with riluzole or not, must be based on the description of the disease course in an individual patient.

The prognosis of the other LMND forms with non-generalized muscle weakness appears to be more favourable, because in our study clinical abnormalities remained confined to the limb(s) in which weakness had started in the majority of patients during follow-up and respiratory insufficiency did not occur. We did not find a significant increase of weakness or functional impairment in the patients with distal SMA, although the group was small. Our study shows that in distal SMA weakness of the arms is more severe, although the arms remain affected in a lesser degree than the legs, than described in previous studies.[80,138] In contrast with distal SMA, we found a significant increase of weakness and functional impairment in patients with segmental distal SMA and segmental proximal SMA. This may point to a slowly progressive disease course and not to a disease course that is stationary after initial progression, such has been described previously.[45,72,87,178,222] In one patient with segmental proximal SMA the diagnosis was changed into ALS. This, together with the slowly progressive disease course that we found, suggests that the segmental LMND forms, like slowly progressive spinal muscular atrophy, should be considered in relation to ALS. Further studies are needed with a greater number of patients and a longer follow-up time to confirm these results.

To conclude, the natural course of sporadic adult-onset lower motor neuron disease is slowly progressive, as we found an increase of muscle weakness and functional impairment during follow-up. Life expectancy may be decreased and UMN signs may develop, such that 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. The results of the present study will be helpful in making a correct diagnosis in these patients after a prolonged observation.

Hereditary pure lower motor neuron disease with adult onset and rapid progression

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Introduction

The familial lower motor neuron diseases (LMND) with adult onset form a heterogeneous group of disorders. These include spinal muscular atrophy (SMA) with autosomal recessive and autosomal dominant mode of inheritance, distal spinal muscular atrophy with autosomal recessive, autosomal dominant or X-linked mode of inheritance, X-linked Kennedy's disease and the rarely described form of scapuloperoneal spinal muscular atrophy (for overview see table 1). The adult onset form of SMA, often described as type IV, is less well defined than the childhood forms (types I- III).[150] Deletions in the survival motor neuron (SMN) gene on chromosome 5 are demonstrated in more than 95% of the childhood autosomal recessive cases of SMA[75,127], whereas in only approximately 30% of the adult patients with an autosomal recessive form this deletion was found.[17,32,52,198,245,247] X-linked Kennedy disease is characterized by androgen receptor dysfunction, caused by a CAG repeat expansion in the first of five exons of the androgen receptor gene.[113,133]

Common to the familial LMND forms with adult onset are the facts that they are characterized by a slowly progressive limb girdle syndrome and are considered to have a benign disease course. By contrast, the disease course of familial amyotrophic lateral sclerosis (FALS), in which both lower and upper motor neurons are affected, is progressive and invariably leads to death.[242] In the present study we report pathological and clinical findings in two families with LMND with adult onset and a rapidly progressive disease course.

Methods

Mutation analysis

DNA was extracted and mutations screened in the survival motor neuron (SMN), copper/zinc superoxide dismutase (SOD1) and androgen receptor genes. Deletions of the telomeric copy of SMN were detected using polymerase chain reaction (PCR) primers specific for exons 7 and 8.[236] Mutations in all five exons of the SOD1, the intron/exon boundaries and 5' and 3' untranslated regions were screened by direct sequencing on an ABI 377. The first exon of the androgen receptor gene was amplified by PCR to determine the number of CAG repeats. The PCR products were loaded on a 5% Longranger/6.0M Urea gel (FMC BioProducts), run on an ABI 377 Automated Sequencer. Product lengths were compared in size using positive and negative controls for the expanded allele.

Table 1. Hereditary lower motor neuron syndromes with adult onset.

	Mode of inher.	*Clinical signs and symptoms*	*Age at onset in decades*	*Study (number of patients)*	*Disease course*	*Resp. involv.*	*DNA abnormalities*
SMA type IV	AR	Symmetrical proximal muscle weakness	2 - 5	Hausmanowa-Petrusewicz (354)[84], Souchon (63)[207], Zerres (445)[246], (569)[247]	Slow	No	Telomeric deletion in SMN-gene
SMA type IV	AD	Symmetrical proximal muscle weakness	3 - 4	Pearn (13)[172], Kausch (36)[112], Rietschel (20)[182], Rudnik-Schöneborn (5)	Mildly progressive	No	Unknown
Distal SMA	AD/ AR	Foot deformity, distal limb (legs >arms) weakness	1 - 4	Harding (34)[80], Boylan (13)[15]	Slow	No	Unknown
Kennedy disease	X-linked	Bulbar weakness + symmetrical proximal muscle weakness	3 - 5	Kennedy (11)[113], Harding (10)[81], Igarashi (19)[93], Amato (17)[5]	Slow	No	Repeat expansion androgen receptor gene
Scapuloperoneal SMA	AD/ AR	Symmetrical distal limb and shoulder girdle weakness and foot deformity	3 - 5	Kaeser (12)[101]	Slow	No	Unknown
FALS with predominant LMN involvement	AD	Asymmetrical distal limb weakness	4 - 6	Rosen (14)[183], Cudkowicz (11)[38]	Rapidly progressive	Yes	SOD 1 - mutation
Scapulohumeral SMA	AD	Muscle weakness neck, shoulder girdle and upper arm muscles	3 - 5	Jansen (3)[98]	Rapidly progressive	Yes	Unknown
Family A	AD	Symmetrical limb-girdle syndrome	3 - 4	-	Rapidly progressive	Yes	Unknown
Family B	AD	Asymmetrical distal limb weakness	6 - 7	-	Rapidly progressive	Yes	Unknown

Inher. = inheritance. Resp. involv. = respiratory involvement. AR = autosomal recessive. AD = autosomal dominant. SMA = spinal muscular atrophy. FALS = familial amyotrophic lateral sclerosis. LMN = lower motor neuron. SMN gene = survival motor neuron gene.

Pathology

Paraffin sections of the motor cortex, midbrain, pons, medulla, spinal cord (at cervical, thoracic, and lumbar levels) were stained with hematoxylin and eosin (HE) and with Klüver-Barrera's stain for myelin. For immunohistochemical analysis (performed in patients 1 and 4) the following primary antibodies were used: to detect macrophages anti-CD68 (monoclonal; Harlan/sera), astrocytes anti-GFAP (Dako), anti-ubiquitin (polyclonal; Dako) and anti-neurofilaments (monoclonal 70kD, 200 kD; Monosan). After incubation with primary antisera the sections were incubated in a biotin-streptavidin protocol using diaminobenzindine as chromogen.

Case histories

Family A

The family pedigree is shown in figure 1.

Patient 1 (figure 1, III-1)

In October 1996, a 39 year old man experienced proximal weakness in both upper limbs. After a few months he noted proximal weakness in both lower limbs, which was followed by weakness of both hands. In June 1997 neurological examination showed severe atrophy of muscles of the shoulder girdle, upper limbs and proximal lower limbs. Weakness in the upper and lower limbs was symmetrical and more pronounced proximally. Widespread fasciculations were seen. Tendon reflexes were decreased or absent and the plantar responses were flexor. Bulbar muscles were spared and no sensory disturbance was detected.

Laboratory features, results of other investigations and results of mutation analyses are shown in table 2. At follow-up, muscle weakness progressed symmetrically in upper and lower limbs. In October 1997, the patient died at the age of 40 from respiratory failure, 12 months after symptom onset.

On postmortem examination the brain and the brainstem, including the medulla oblongata, were normal at the macroscopic level. Light microscopy revealed no signs of neuronal breakdown in the precentral and postcentral gyri. Betz cells were present and normal. The corticospinal tracts were normal, as were the appearance and numbers of motor neuron cells in the brainstem nuclei (IX, X, XI, XII). No gliosis was seen in the brain stem. Immunohistochemistry revealed no accumulation of CD 68-positive macrophages in precentral gyri, corticospinal tracts or brain stem. Anti-neurofilament and anti-ubiquitin staining did not show any abnormalities. The spinal cord was not available.

Patient 2, brother of patient 1, (figure 1, III-2)

In 1998, a 35-year-old man presented with fasciculations in upper and lower limbs. Initially, no abnormalities were found on either neurological examination or elec-

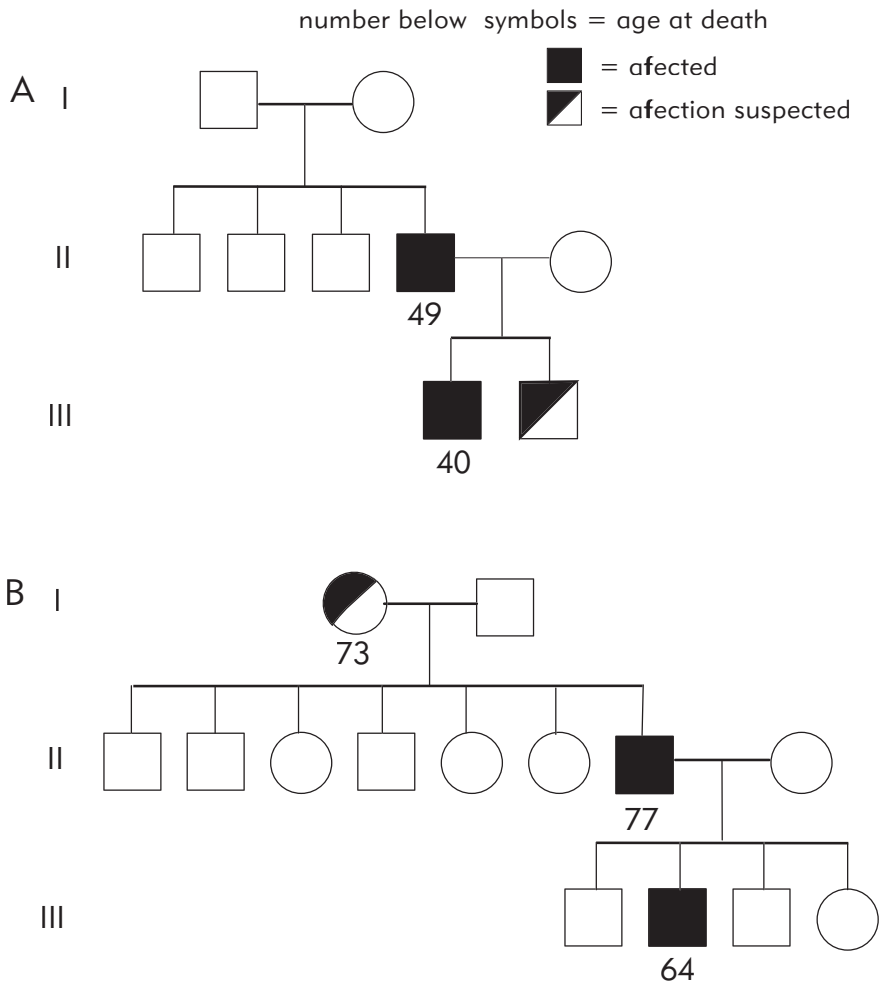

Figure 1. Family pedigree of family A and B.

tromyography. In 2000 he noticed weakness in the right shoulder and on neurological examination a symmetrical proximal paresis of the upper limbs was found. A similar diagnosis as in patients 1 and 3 is suspected. Laboratory features are shown in table 2.

Patient 3, father of patient 1 and 2, (figure 1, II-4).
In 1965, a 46-year-old man developed symmetrical proximal weakness of the upper and lower limbs. The disease progressed to almost complete paralysis excluding the facial muscles and distal upper limbs. In 1968, he had a severe upper respiratory tract

infection necessitating artificial ventilation and a temporary tracheostomy. He recovered but died six months later from respiratory failure.
Postmortem examination was performed in 1968. Spinal cord examination for this study was only possible using the original sections. Degeneration of the corticospinal tracts was not present (figure 2.1). There was considerable loss of motor neuron cell nuclei in all segments. A single ballooned neuron was observed in both the cervical and lumbar segments with slight chromatolysis. Neuronophagia and gliosis were clearly present (figures 2.2 and 2.3).

Family B
The family pedigree is shown in figure 1.
Patient 4, (figure 1, III-2)
In 1992, a 60-year-old man experienced a left-sided foot drop. In December 1993 he noted weakness of the left hand. The neurological examination revealed atrophy and weakness of the left thumb and intrinsic hand muscles. Profuse fasciculations were seen in both legs. There was atrophy of muscles of the left lower leg and foot with weakness of foot dorsiflexion and plantarflexion The tendon reflexes were reduced or absent. There were no bulbar or pyramidal signs or sensory disturbances. Laboratory features, results of other investigations and results of mutation analyses are shown in table 2. Gradually weakness progressed to involve muscles of the right foot, right hand and to the lower limbs more proximally. Walking became increasingly difficult. In April 1997, the patient died from respiratory failure, five years after symptom onset.
At autopsy the brain appeared normal macroscopically, but the anterior spinal roots were thinner than expected. Light microscopy revealed no abnormalities in the brain or brainstem. By contrast, many changes were found in spinal cord neurons. In the cervical segments, loss of motor neurons in the anterior horns was obvious and sporadic axonal swelling and gliosis were seen. In the lumbar segments there was considerable loss of motor neurons, surviving neurons had swollen cytoplasm and swollen proximal axons. Longitudinal sections revealed eosinophilic neuronal inclusions (Bunina body, figure 2.4). Many macrophages were seen in the anterior horns especially in the lumbar region. These were absent in the corticospinal tracts or in the neocortex. Swollen axons in longitudinal sections of the spinal cord stained positive for neurofilaments (figure 2.5). Anti-ubiquitin staining revealed dense intraneuronal cytoplasmic inclusions in longitudinal sections of motor neurons in the lumbar part of the spinal cord (figure 2.6).

Table 2. Clinical, laboratory features, other investigations and results mutation analysis of patients

	Family A			*Family B*	
	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
Clinical features					
Sex	Male	Male	Male	Male	Male
Age at onset (years)	39	37	46	60	75
Site of onset	proximal weakness of upper limbs	proximal weakness of upper limbs	proximal weakness of upper & lower limbs	left foot drop	amyotrophy limbs, followed by bulbar symptoms
Age at death (years)	40	NA	49	64	77
Laboratory features					
Creatine kinase (<180 U/L)	elevated (921)	elevated (285)	NA	NA	NA
Electrolytes including calcium	normal	normal	NA	normal	NA
Agar electrophoresis	normal	NA	NA	normal	NA
Other investigations					
MR-imaging cervical & lumbar spinal cord	NA	normal	NA	normal	NA
Electromyography	Fipo's	Fipo's	NA	Fipo's	NA
Nerve conduction studies	normal*	NA	NA	normal*	NA
Motor evoked potentials	normal	NA	NA	NA	NA
DNA results					
Deletion SMN-gene	no	NA	NA	no	NA
Mutation SOD1-gene	no	NA	NA	no	NA
Repeat expansion AnR-gene	no	NA	NA	no	NA

*NA = not available. Fipo's = fibrillations and positive waves in arm and leg muscles. * = no evidence of demyelination or conduction block was found. SMN-gene = survival motor neuron gene. SOD1-gene = superoxide dismutase 1 gene. AnR-gene = androgen receptor gene.*

Patient 5, father of patient 3, (figure 1, II-7)
In 1976, a 75-year-old man developed weakness and atrophy of the limbs, followed by dysarthria and dysphagia. At that time, upper motor neuron signs were not apparent and a diagnosis of LMND was made. Two years later he died from respiratory weakness. Further data are missing and autopsy was not performed. The mother of this patient (patient 6, figure 1, I-1) was reported to have suffered from a similar disease. She died at the age of 73 years.

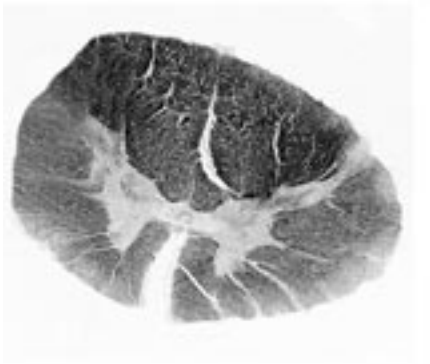

figure 2.1: (17x) no signs of degeneration of the corticospinal tracts

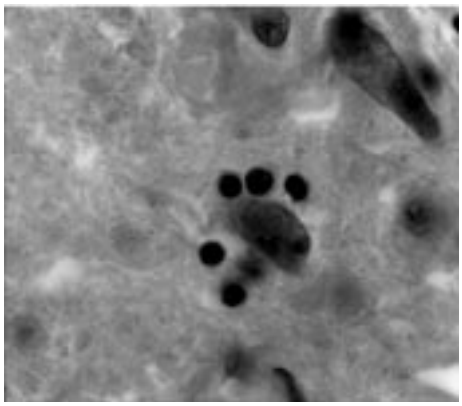

figure 2.2: (500x) neuronophagia of anterior horn cell

Figure 2. Pathological findings
Transverse sections of patient 3 with Klüver-Barrera's staining method for myelin in thoracic spinal cord (figure 2.1), and a hematoxylin and eosin staining in cervical spinal cord (figures 2.2 and 2.3).

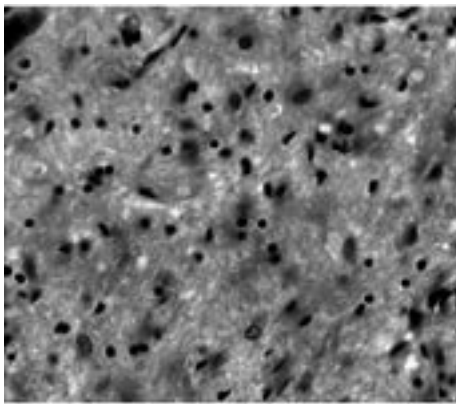

figure 2.3: (280x) gliosis in the anterior horn

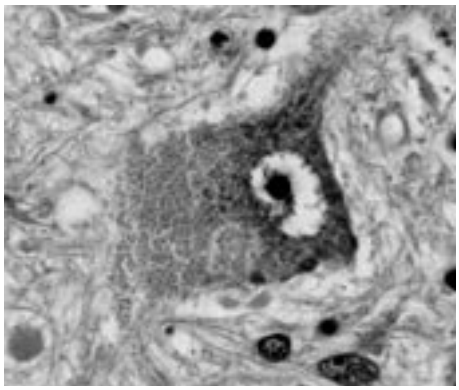

figure 2.4: (800x) Bunina body

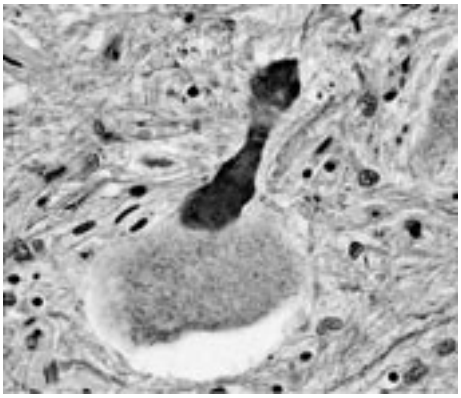

figure 2.5: (590x) axonal swelling in proximal part of an axon

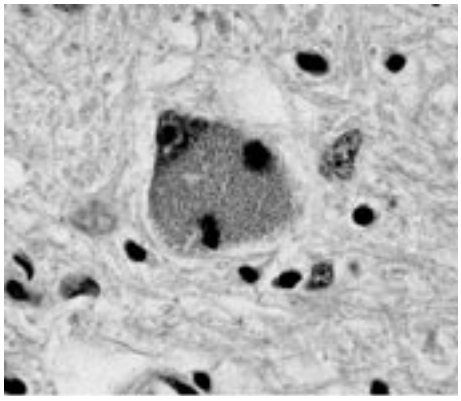

figure 2.6: (670x) cytoplasmic intraneuronal ubiquitin-positive inclusions

Figure 2. Pathological findings (continued) Longitudinal sections of lumbar spinal cord in patient 4 stained by hematoxylin and eosin (figure 2.4), anti-neurofilament (figure 2.5) and anti-ubiquitin (figure 2.6).

Discussion

These patients had rapidly progressive motor neuron disease (MND) without clinical or pathological evidence of upper motor neuron involvement. As death followed one to five years after onset of symptoms, progression was as rapid as in FALS or sporadic ALS (SALS).[85,100,157] Autosomal dominant transmission of disease is favoured by male to male inheritance in both families (excluding an X-linked condition) and the fact that in family B three generations were possibly affected. In addition, late onset is an argument against autosomal recessive inheritance.[43] An alternative explanation could be inheritance through three independent recessive

mutations. This would appear as pseudo-dominant inheritance if carrier frequencies of the recessive allele are high, as can occur in chromosome 5-linked SMA.[187] However, the absence of a deletion of the telomeric part of the SMN gene ruled out autosomal recessive or pseudodominant inheritance of this type of SMA. Families A and B differed in regard to the pathological findings in the spinal cord. In family A pathological changes were found characteristic of SMA whereas in family B specific neuronal changes were found that also occur in patients with ALS.

There is little information on the cellular pathology of adult-onset SMA. In the anterior horns of the spinal cord of patient 3 of family A we found a few ballooned neurons with slight chromatolysis that have been regarded a characteristic pathological feature of infantile-onset SMA.[125,151] We also have observed neuronophagia and gliosis that also have been described in pathological studies of SMA.[151] Although the pathological examination in family A is not complete, we think that the lacking of corticospinal tract involvement and axonal swelling in the spinal cord of patient 3 and the negative anti-neurofilament and anti-ubiquitinin staining of the brain of patient 1 make a pathological diagnosis of (F)ALS unlikely and suggest the possibility of a disease form that shows some similarities with SMA. Furthermore, the members of family A presented with a symmetrical limb girdle syndrome, similar to what has been described in autosomal dominant SMA. We therefore think that the autosomal dominant form of lower motor neuron degeneration of family A shows some similarities with autosomal dominant SMA.

Autosomal dominant SMA was initially classified into a childhood/juvenile and an adult onset form, which were generally considered to reflect two clinical and genetic entities[172] representing less than 2%, and approximately 30% of SMA cases. The adult onset form of autosomal dominant SMA may manifest in the third or fourth decade with progressive proximal muscle weakness. Patients lose the ability to run within five years of onset, but median life expectancy has been found to be 20 years. Later, Rietschel described intermediate forms of autosomal dominant SMA in which both pattern of muscle involvement and ages of onset vary more than described by Pearn in his proposed classification.[182] However, disease progression was mild and life expectancy was normal in the cases of these intermediate forms, and thus different from our family A. A disease course that is comparable with family A has been described by Jansen et al. in a kindred with an autosomal dominant scapulohumeral form of SMA. (see table 1).[98] The three affected members of this family showed weakness of muscles in the neck, shoulders and upper arms combined with progressive respiratory insufficiency, but had no signs or symptoms in the lower limbs. Because the lower limbs were affected in the two deceased patients of family A, this autosomal dominant form of lower motor neuron degeneration may concern a new disease variant. This suggests genetic heterogeneity of the auto-

somal dominant and symmetrical disease forms that are known within the spectrum of MND and has implications for genetic counselling.

The pathological observation of neuronal changes, like ubiquinated inclusions, Bunina bodies and axonal swelling in the spinal cord of patient 4 is similar to what has been observed in ALS (www.wfnals.org). Ubiquinated neuronal inclusions in lower motor neurons (LMN) of spinal cord and brain stem are regarded as a highly significant correlate of the diagnosis of ALS[94] and usually are more abundant than Bunina bodies.[129] Bunina bodies are small (1-10 μm) eosinophilic cytoplasmic inclusions of unknown molecular composition, found in anterior horn cells in up to 70% of FALS and SALS cases.[129] Both neuronal inclusions may be the result of molecular abnormalities that develop during degeneration of vulnerable lower motor neurons. Recently, ubiquinated neuronal inclusions have also been reported in the brain stem and spinal cord of sporadic patients with progressive spinal muscular atrophy (PSMA), a form of MND with predominantly LMN signs.[94] Moreover, pathological studies on patients with PSMA usually reveal subclinical involvement of the corticospinal tracts, further supporting the hypothesis that PSMA and ALS are pathologically linked.[165] The finding of pathological features that occur in both (F)ALS and PSMA, together with the clinical presentation (distal asymmetrical muscle weakness in patient 4 and bulbar signs in patient 5) and the high age at onset (60 and 75 years) may be suggestive for a diagnosis of FALS.

Knowledge of the genetic background of FALS is increasing as already more than 60 different mutations in the SOD1 gene have been discovered.[200] Also different genotypes are correlating increasingly with clinical features of patients with FALS.[179] Limited corticospinal tract involvement and predominant LMN involvement in FALS have been associated with five mutations in the SOD1 gene. The most frequent of these five mutations is the A4V mutation, the most common SOD1 mutation worldwide.[38,204] The A4V mutation is associated with a short disease duration of approximately one year.[100,183] Recently, Cudkowicz et al. reported both clinical and pathological features of 11 A4V-positive FALS patients. Clinically, they found only LMN signs in 10 of 11 patients. On pathological examination in five patients, four patients showed evidence of LMN involvement with sparing of Betz cells and only mild changes in the corticospinal tracts.[38] These authors propose that the diagnostic criteria for FALS should be further broadened and should include patients with a SOD1 mutation, who show only LMN involvement. In family B no SOD1 mutations were detected, but these account for only 20% of all autosomal dominant FALS cases.[200] Other genes are presumably responsible for the remainder. Hence a currently unknown FALS gene may exist in family B, exhibiting phenotypic similarity to A4V- SOD1.

These patients demonstrate that confusion between the diagnoses of SMA, PSMA

and FALS can arise, especially with disease onset in adulthood. We conclude that the disease variants seen in our two families may further broaden the spectrum of LMND.

Mimic syndromes in sporadic cases of progressive spinal muscular atrophy

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Introduction

Progressive spinal muscular atrophy (PSMA) is a nonhereditary progressive disease of the lower motor neurons (LMN). This disease entity has been described under various names. In 1850, Aran first reported this disease, which he called "progressive muscular atrophy".[6] Progressive muscular atrophy was later termed "progressive spinal muscular atrophy".[244] Because a proportion of these patients eventually develop clinical signs of upper motor neuron (UMN) degeneration or show UMN pathology at autopsy, PSMA and ALS are often considered part of a clinical spectrum. Therefore, in the United Kingdom and elsewhere, PSMA and ALS are often termed "motor neuron disease" (MND).[242]

PSMA may run a rapidly progressive course comparable with that of ALS or may have a slowly progressive course over many years. Focal types have been described.[48,87,206,209]

In 1994, the El Escorial criteria based on clinical, and electrophysiological features were proposed for ALS. These criteria define four categories: definite, probable, possible, and suspected. In the 1994 El Escorial criteria, PSMA met the criteria for suspected ALS.[19] Within the 1998 revised El Escorial criteria, PSMA is no longer present (**www.wfnals.org**). However, familial ALS (Ala4Val SOD mutation) may present as a lower motor neuron syndrome.[38] Recent studies showed that less severe or even treatable diseases can mimic early MND.[42,219] In particular, multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) should be differentiated from PSMA.[175,225,231]

We describe patients initially included in a follow-up study on sporadic cases of PSMA in whom the initial diagnosis of PSMA proved to be incorrect.

Patients and methods

In 1998 the Academic Medical Center and the University Medical Center Utrecht started a joint prospective study on the natural history and prognosis of PSMA. Consecutive patients with a prior diagnosis of PSMA were asked to participate in the study. All patients had been diagnosed by experienced neurologists. We selected patients by screening of the files of both outpatient neuromuscular departments for all patients diagnosed as having PSMA, focal SMA, segmental SMA, and lower motor neuron disease (LMND). Nine patients were recruited from other hospitals.

All patients underwent re-appraisal before inclusion. They were seen at different stages of their illness. Inclusion criteria of the natural history PSMA study were (1) clinical signs of LMN involvement (weakness, atrophy, and fasciculation) in one or

more of the four regions (bulbar, cervical, thoracic, lumbosacral) according to the 1994 El Escorial criteria and (2) electrophysiological evidence of LMN involvement in clinically affected and nonaffected regions without evidence of conduction block (CB) (see below). Exclusion criteria were (3) objective sensory signs (apart from mild vibration sense disturbances in elderly patients), (4) a history of diseases that may mimic MND (i.e., spinal radiculopathy, poliomyelitis, diabetic amyotrophy), (5) family history of inherited SMA, and (6) definite symptoms and signs of UMN involvement (Babinski sign, pseudobulbar symptoms, and (sub)clonic reflexes). Patients in whom the diagnosis of PSMA had to be rejected on the basis of one or more of these criteria are the subject of this article.

Obligatory ancillary investigations. The following laboratory tests were performed: sedimentation rate, hemoglobin, hematocrit, thyroid-stimulating hormone, serum protein electrophoresis, and serum immunoelectrophoresis with immunofixation, phosphate, calcium (and, if elevated, parathyroid hormone), and serum IgM anti-GM1 antibodies. If appropriate neuroimaging studies were lacking (either spinal cord myelography with CT or MRI), MRI of the craniocervical junction or pertinent spinal cord was performed. If patients met criteria for adult SMA or Kennedy disease, DNA analysis was performed.[17,64] If an alternative diagnosis was suspected, specific ancillary investigations were performed, such as muscle biopsy, serum creatine kinase activity, electromyography (EMG) with repetitive stimulation, and anti-acetylcholine receptor (anti-AChR) antibodies.

Electrophysiological studies. The electrophysiological investigation took place after warming the limbs in water at 37 °C for at least 30 minutes.[67] Motor nerve conduction on both sides was investigated up to Erb's point in the median (recording: abductor pollicis brevis and flexor carpi radialis muscles), ulnar (recording: abductor digiti minimi muscle), radial (recording: extensor carpi ulnaris muscle), and musculocutaneous (recording: biceps brachii muscle) nerves and up to the popliteal fossa in the deep peroneal (recording: extensor digitorum brevis muscle) and tibial (recording: abductor hallucis muscle) nerves. Sensory conduction on distal stimulation was investigated in at least one median and sural nerve. In case of motor CB in the median or ulnar nerve, sensory conduction was measured over the affected segment. EMG was performed on biceps brachii, flexor carpi radialis, interosseus dorsalis I, rectus femoris, tibialis anterior, and gastrocnemius (lateral head) muscles and on one side in the erectores spinae at Th6 and Th10 levels. We measured the amplitude and area of the negative part of each compound muscle action potential (CMAP). We defined definite CB as an area reduction on proximal versus distal stimulation (P/D) of at least 50% and probable CB as amplitude reduction P/D of at least 30% in an arm nerve.[2,181]

Results

From a total of 89 patients who were referred for the PSMA prospective study, in 17 (19%), PSMA turned out to be an incorrect diagnosis. Table 1 shows the diagnoses, clinical features and reasons for diagnostic revision in the 17 patients with a mimic syndrome. There were 13 men (76%) and women (24%). The median age at the current analysis was 58 years (range 33 to 89 years). Age at onset ranged between 23 and 87 years (median 50 years). Disease duration ranged between 1 and 25 years (mean 10 years). After thorough electrophysiological analysis, MMN was demonstrated in seven patients and CIDP in two. Other treatable diagnoses were autoimmune limb girdle MG (n = 1) and inflammatory myopathy (n = 1). Six of 17 patients (30%) had untreatable diseases: idiopathic chronic axonal polyneuropathy, idiopathic brachial plexus neuropathy, syringomyelia, and myopathy. One patient with a possible herniated lumbar disk recovered spontaneously, and only one patient had slowly progressive ALS.

Case reports

A 50-year-old man presented in 1992 with weakness and minimal atrophy of arms and legs without ocular or bulbar symptoms. EMG in 1993 showed fibrillations, complex repetitive discharges, and polyphasic longduration motor unit action potentials (MUAP) in proximal and distal arm and leg muscles. Motor and sensory conduction studies revealed no abnormalities. A diagnosis of PSMA was made. In 1999 he was reviewed for the natural history study. During this time, his weakness had become remarkably exertion dependent. EMG in 1999 showed complex repetitive discharges and occasionally positive sharp waves in the deltoideus, trapezius, iliopsoas, and paraspinal muscles. Slight voluntary effort elicited small polyphasic MUAP, and maximum voluntary effort a severely reduced pattern or a low-amplitude full pattern. Repetitive stimulation with 3 Hz that was performed because of the exertion dependence revealed CMAP amplitude decrement of 12% in the abductor digiti minimi muscle and of 19% in the trapezius muscle. Although the absence of ocular and bulbar symptoms does not support a diagnosis of MG, anti-AChR antibodies were found, and the diagnosis of chronic limb girdle MG was made.[161] Weakness improved on pyridostigmine.

A 42-year-old man presented in 1981 with purely LMN signs in the arms, confirmed by electrophysiology, and was diagnosed as having segmental SMA. At reassessment for our study in 1999, he displayed generalized weakness in all extremities with additional dissociated sensory loss in the arms and a pyramidal syndrome of

the lower limbs. MRI showed an extended syrinx from the cervical into the thoracic cord (figure).

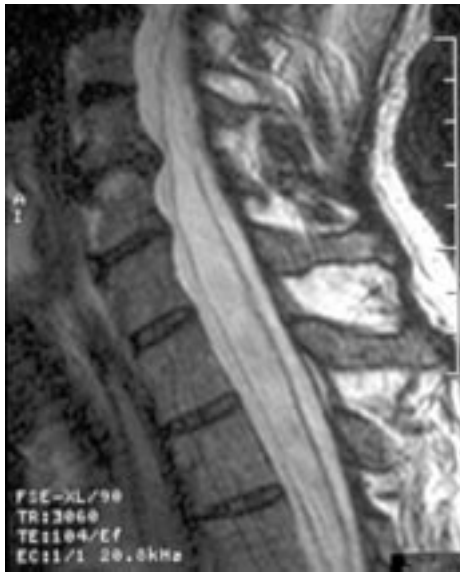

Figure. T2-weighted MR image shows extended syrinx from cervical into thoracic spinal cord.

A 61-year-old man presented with a 1-year history of weakness of arms and legs. On re-examination, there were tetraparesis, proximal more than distal, and atrophy of particularly the shoulder girdle muscles. EMG at presentation in 1999 showed fibrillations and positive sharp waves and polyphasic MUAP of low or high amplitude in proximal and distal arm and leg muscles. These findings, in combination with weakness and wasting of all limbs, were thought consistent with a diagnosis of PSMA. EMG in 2000 showed fibrillations and positive sharp waves in the biceps brachii, flexor carpi radialis, iliopsoas, rectus femoris, tibialis anterior, and gastrocnemius muscles. In most of these muscles, light voluntary effort elicited low-amplitude, short-duration, polyphasic MUAP with greatly increased recruitment and maximum voluntary effort a low-amplitude full pattern. Nerve conduction studies were normal, except for severe conduction slowing consistent with demyelination across the fibular head segment of the right peroneal nerve. As this examination was consistent with myopathy and as serum creatine kinase level was elevated (852 IU/L; upper limit of normal 190 IU/L), a muscle biopsy was performed. Muscle biopsy of the left biceps brachii revealed marked variation in the size of muscle fibers, numerous necrotic fibers (some undergoing phagocytosis), occasional regenerating fibers, a few small mononuclear cell infiltrates localized around small blood vessels in the perimysium, many clumps of nuclei, and the occasional atrophic fiber, moth-eaten fiber, and ragged red fiber. Rimmed vacuoles were not present. Since the patient reported spontaneous improvement, no treatment has been given. Nevertheless, he still displays evident muscle weakness and atrophy.

A 33-year-old man presented with weakness and atrophy of the right abductor pollicis brevis and interosseus dorsalis I muscle. In 1993 nerve conduction studies revealed neither CB nor demyelinating features, and the diagnosis of juvenile muscular atrophy of the distal upper limb (Hirayama disease) was made. In 1998 extensive nerve conduction studies revealed CB of the right median nerve in the upper

Table 1. Clinical features of 17 patients with PSMA mimic syndromes

Diagnosis	*Age (yrs)*	*Dis. dur (yrs)*	*Response to therapy*	*Weakness*	*Sensory signs*	*Reflexes*	*Electrophys. examination*	*Other ancill. investigation*	*Reasons for diagnostic revision*
ALS	67	15	-	prox = dist	no	plantar responses extensor	no abnorm.	-	atypical symptoms / ancill. investigation
myasthenia gravis	49	7	yes	prox = dist	no	normal	decremention	AchR-AB +	atypical symptoms / ancill. investigation
syringomyelia	42	18	-	dist > prox	yes	absent in UL / hyperrefl. in LL	no abnorm.	syrinx at MRI	ancill. investigation
myositis	61	1	-	prox > dist	no	normal	small MUPs	CK = 852 U/L	ancill. investigation
idiopathic plexus brachialis neuropathy	58	6	yes	prox	no	asymm. arm	large MUPs	-	no deterioration
myopathy e.c.i.	41	8	-	prox > dist	no	normal		muscle biopsy: myopathic Δ	ancill. investigation
herniated lumbar disk	62	13	-	no	no	normal		-	no deterioration
CIAP	88	3	-	dist > prox	yes	absent	low CMAPs + SNAPs legs	-	ancill. investigation
CIDP	64	6	-	dist > prox	yes	absent ankle	low CMAPs	-	ancill. investigation
CIDP	38	10	no	dist > prox	no	absent ankle	low CMAPs / demyelin	-	ancill. investigation
MMN	47	25	-	dist > prox	no	asymm. arms	CB	-	ancill. investigation
MMN	55	9	yes	dist > prox	no	asymm. / absent	CB	-	ancill. investigation
MMN	50	19	yes	dist > prox	no	absent	CB	-	ancill. investigation
MMN	36	2	unknown	prox = dist	no	absent right arm	CB	-	ancill. investigation
MMN	34	4	yes	dist > prox	no	asymm. / absent	CB/ low CMAPs	_ anti-GM1 AB	ancill. investigation
MMN	52	16	yes	prox = dist	no	asymm. / absent	CB/ low CMAPs	_ anti-GM1 AB	ancill. investigation
MMN	33	6	no	dist > prox	no	normal	CB	-	ancill. investigation

Dis. dur. = disease duration. Electrophys. = electrophysiological. Ancill. = ancillary. ALS = amyotrophic lateral sclerosis. CIAP = chronic idiopathic axonal polyneuropathy. CIDP = chronic idiopathic demyelinating polyneuropathy. MMN = multifocal motor neuropathy. Prox = proximal. Dist = distal. UL = upper limb. LL = lower limb. Hyperrefl. = hyperreflexia. Asymm. = asymmetrical. MUP = motor-unit potential. CMAP = compound muscle action potential. Demyelin. = signs compatible with demyelination. CB = conduction block. AchR = achetylcholinereceptor. AB = antibodies. CK = creatine kinase. Δ = changes.

arm segment, and the diagnosis was modified to MMN. Owing to the slow progression of signs and symptoms and minimal weakness, the patient has not been treated with IV immunoglobulin.

Discussion

Our prospective study on patients with PSMA aimed at establishing prognostic determinants and the course of the disease. Following careful reexamination of patients with this diagnosis before inclusion into our study, 17 patients (19%) were ultimately rediagnosed with conditions other than PSMA. PSMA was still the correct diagnosis in the other 80% of patients, but these patients are subjects of a separate report.

The frequency of misdiagnoses in MND was analyzed in the Scottish Motor Neuron Disease Register. In 8% (46/552), an alternative diagnosis was made. In a study on Irish ALS patients, a percentage of 7.3% (32/437) misdiagnoses was reported.[42,196,219] However, these studies are not entirely comparable with our study because the methodologies are different. Both the Scottish and the Irish study concentrated mainly on patients with ALS, whereas we focused on patients with PSMA. The Scottish and Irish studies reported mainly on recently diagnosed patients, whereas in our study, the majority of patients had a longer disease duration. As a consequence, the patients with a lower motor neuron form of ALS (either PSMA with rapid progression or PSMA turning into ALS) have already been filtered from our group. Our study is thus dealing with patients with PSMA that has not evolved into ALS after a certain period, except for one patient with a slowly progressive form of ALS. Our study yielded a high percentage of MMN (41%) as compared with 4% in the Scottish study and 22% in the Irish study. This can be explained by our selection of patients with pure lower motor neuron syndromes and by our extensive and standardized electrodiagnostic protocol.

Previously performed electrophysiological examination has contributed to the wrong diagnosis in a number of our patients. In two patients, a typical myopathic pattern on EMG consisting of spontaneous muscle fiber activity, low-amplitude, short-duration, polyphasic MUAP, and increased recruitment was not recognized as such. The diagnosis of MMN was missed either because the entity was not known at the time of the first investigation, or possibly because an insufficient number of nerves was examined. An extensive examination is often necessary to detect CB. In a previous study, we have shown that in 12 of 21 patients with definite MMN, CB was detected in only one nerve segment, despite our extensive protocol.[231]

Our study shows that patients with PSMA should be followed up meticulously in

order to detect development of features or a course not consistent with PSMA. Tailored investigations should then be performed to establish the correct diagnosis and, in particular, to identify potentially treatable disorders.

Multifocal motor neuropathy: diagnostic criteria that predict the response to immunoglobulin treatment

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Introduction

Multifocal motor neuropathy (MMN) is characterized by slowly progressive, asymmetric weakness of limbs without sensory loss. Substantial evidence for an immune-mediated pathogenesis has led to various studies of immunological treatment of MMN.[26,28,63,117,131,153,171,176,226,243] Treatment with high-dose intravenous immunoglobulins (IVIg) is at present the established therapy for MMN. As MMN has proven to be a treatable disorder, its differentiation from lower motor neuron disease (LMND) is important. Evidence of conduction block is considered one of the relevant criteria for the diagnosis of MMN. Strict criteria for conduction block have been used to avoid misinterpretation due to phase cancellation that may be a feature of motor neuron disease (MND). However, previous studies have suggested that criteria requiring strict evidence of conduction block may lead to underdiagnosis of this potentially treatable neuropathy.[58,111] On the other hand, clinical or laboratory features that may differentiate patients with MMN from patients with LMND have not been clearly defined.

Using a standardized examination, we studied the clinical, laboratory and electrophysiological characteristics of 37 patients presenting with lower motor neuron syndromes and electrophysiological features compatible with segmental 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 IVIg treatment.

Patients and methods

Patients

In a prospective study from 1996 to 1999, we included patients on the basis of two criteria: (1) a lower motor neuron syndrome and (2) electrophysiological evidence of conduction block (CB) or features other than CB compatible with demyelination (see below). Patients who had bulbar signs or symptoms, or upper motor neuron signs (spasticity, hyperreflexia, extensor plantar response) were excluded. Mild sensory symptoms were permitted as long as there were no sensory deficits on examination, and sensory nerve conduction studies were normal. All patients were tested for serum IgM anti-GM1 antibodies as described elsewhere.[228] For each patient, the number of affected limb regions (upper arm, lower arm, upper leg, lower leg on the left or right side; maximally eight regions) was determined before treatment with IVIg and at the last neurological examination. Magnetic resonance (MR) imaging of the brachial plexus was performed according to a protocol described previously.[237]

Electrophysiological studies

Nerve conduction on both sides was studied by the same investigator (HF) using a standardized protocol and surface electrodes.[225] Motor nerve conduction was investigated up to Erb's point in the median (recording: m. abductor pollicis brevis, m. flexor carpi radialis), ulnar (recording: m. abductor digiti V), radial (recording: m. extensor carpi ulnaris) and musculocutaneous (recording: m. biceps brachii) nerves and up to the popliteal fossa in the deep peroneal (recording: m. extensor digitorum brevis) and tibial (recording: m. abductor hallucis) nerves. Antidromic sensory conduction was investigated in the median, ulnar, radial, and sural nerves. In case of motor conduction block in the median or ulnar nerve, sensory conduction was measured over the affected segment. F waves were recorded after 20 distal stimuli to the median, ulnar, deep peroneal and tibial nerves. Prior to an investigation, the arms and legs were warmed in water at 37° C for at least 30 minutes; thereafter they were kept warm by infrared heaters.[67] From each compound muscle action potential (CMAP) we measured the amplitude, duration and area of the negative part. We scored for a nerve: distal CMAP amplitude, amplitude reduction (%), area reduction (%) and duration prolongation (%) of the CMAP on proximal versus distal stimulation (P/D)[232]; for each segment: distal motor latency (DML), motor conduction velocity (MCV) and shortest F - M latency; and for each patient mean distal amplitude (mV).

Conduction abnormalities were categorized into: (1) definite conduction block (CB) (area reduction P/D ≥ 50% in a long segment or amplitude reduction P/D ≥ 30% over 2.5 cm[66,181], (2) probable CB (amplitude reduction P/D ≥ 30% in an arm nerve)[2,160]; (3) features other than CB compatible with demyelination (MCV decreased below 75% of the lower limit of normal, DML or F - M latency increased above 130% of the upper limit of normal, or absent F waves).[66] Distal CMAP amplitude was at least 1 mV for CB and 0.5 mV for the features other than CB compatible with demyelination. Evidence of demyelination at entrapment sites[66] was not scored. Responses were only scored if stimulation was 20% (Erb's point: 30%) above the strength yielding a maximal CMAP. In case of CB, we ensured that the proximal CMAP did not increase by setting the stimulator at maximal output. If necessary, a collision technique was used to detect effects of co-stimulation.[115,223]

Treatment

All patients were treated with IVIg (0.4 g/kg for 5 days) (Gammagard, Hyland Baxter). Muscle strength was measured by hand-held dynamometry in clinically weak muscles, bilaterally in proximal muscle groups (arm abduction, elbow flexion, elbow extension, hip flexion, knee extension and knee flexion) and distal muscle groups (wrist extension, wrist flexion, ankle dorsiflexion, ankle plantarflexion and

grip strength of the hands) before treatment and two to three weeks after treatment. The values obtained by hand-held dynamometry (in Newtons) were used to assess the response to treatment as described previously[226] : a patient was defined as a 'responder' when muscle strength or grip strength improved by 50% or more in at least two clinically affected muscle groups, without a decrease of 25% or more in muscle strength in more than one muscle group. Follow-up has been assessed by repeated MRC grading and hand-held dynamometry.

Statistical analysis

The Mann-Whitney U test for continuous variables and Fisher's Exact test for categorical variables were used to compare clinical, laboratory and electrophysiological findings between the group of responders and non-responders. With the variables that were significant after univariate testing, a stepwise forward logistic regression analysis was performed. In the comparison between different electrophysiological criteria, a Chi-square test was used with a p-value developed by Monte Carlo simulation of the exact distribution of the test statistic (StatXact 3). A p-value < 0.05 was considered to be significant.

Results

Patients

Thirty-seven patients (30 men, 7 women) were selected (table 1). In 22 patients the upper limbs were first affected and in 15 patients the lower limbs. In 10 of these 15 patients the upper limbs became predominantly affected during the course of the disease. The initial diagnoses that were reached before referral to our hospital varied from MND (15 patients), mononeuropathy (6 patients), polyneuropathy (4 patients), radiculopathy (3 patients), MMN (2 patients), myopathy (1 patient), plexopathy (1 patient) to unknown (5 patients). Twenty-three patients (62%) responded favourably to IVIg.

Electrophysiological studies

In 21 patients definite CB was found in at least one segment (43 segments; range 1 - 6) (table 2). In 30 patients probable CB was found in at least one segment (84 segments; range 1 - 13); in 12 of these patients no definite CB was found. Features other than CB compatible with demyelination were found in 31 patients and occurred in nerves with or without CB. In four patients only features other than CB compatible with demyelination were found.

Table 1. Differences in clinical and laboratory features between responders and non-responders

	Responders	*Non-responders*	*p-value*
Clinical features			
Gender (male/female)	19/4	11/3	NS
Age at onset (mean ± SD; range (yrs))	35.1 ± 9.1; 20 - 58	46.0 ± 16.3; 22 - 74	< 0.05
No. of patients with disease onset upper limbs (n(%))	13 (57%)	9 (64%)	NS
Disease duration (mean ± SD; range (yrs))	8.5 ± 4.3; 2 -17	8.2 ± 9.3; 1-36	NS
No. of affected regions before treatment (mean + SD; range)	3.3 ± 1.3; 2 - 6	5.1 ± 2.1; 2 - 8	< 0.05
Laboratory features			
CSF protein content [1]> 0,5 g/L (n(%))	7 (39%)	3 (60%)	NS
Elevated anti-GM1 antibodies[2] (n(%))	7 (30%)	0 (0%)	< 0.05
CK[3] > 180 U/L (n(%); range of CK)	7 (30%); 43 - 533	10 (83%); 155 - 688	< 0.05
Abnormal MR imaging brachial plexus[4] (n(%))	10 (48%)	3 (30%)	NS
Electrophysiological features			
Percentage of segments with definite CB (mean ± SD)	6.2 ± 6.9	1.4 ± 2.5	< 0.05
Percentage of segments with probable CB (mean ± SD)	10.0 ± 9.1	5.9 ± 7.0	NS
Percentage of segments with demyelination (mean ± SD)	8.7 ± 6.8	6.6 ± 4.9	NS
Mean distal amplitude in mV (mean ± SD; range)	7.1 ± 1.9; 4.6 - 10.6	5.5 ± 1.7; 2.6 - 9.3	< 0.05

SD = standard deviation. NS = not significant. No. = number. CSF = cerebrospinal fluid. GM1= ganglioside GM1. CK = creatine kinase. Abnormal MR imaging plexus brachialis = swelling and/or increased signal intensity. [1] = investigated in 23 patients. [2] = investigated in 34 patients. [3] = investigated in 35 patients. [4] = investigated in 31 patients. CB = conduction block. Demyelination = features other than CB compatible with demyelination.

Table 2. Nerves with conduction block or other features compatible with demyelination

Patient no.	*Definite CB*	*Probable CB*	*Features compatible with demyelination*	
			CV/DML	*F-waves*
1*	Med, Med^{F} 2, Uln, Mus, **Tib**	Uln 3, **Rad**	Uln 2	Uln
2*	Med, **Med^{F}**, Med^{F}, Uln, Rad, **Tib**	**Med**, **Uln**	Uln 2	Med, Uln, Tib, Per
3*	Med, Med^{F}, **Uln**, Mus	Med, Rad	-	Uln
4*	Med^{F}, Uln 2, Tib	Med, **Med^{F}**, Med^{F}, **Rad**	Uln 2	Tib
5*	**Uln 2**, **Tib**	-	Uln	Uln, Per
6*	**Uln**, Uln	**Rad**, Rad, Mus 2	-	Uln, Tib, Per
7*	Med, Tib	Med, Rad	-	Med, Uln, Per
8*	Med, Med^{F}	Med^{F}, **Uln**	Med 3	-
9*	**Med**	**Med**, **Uln**	Med 2, Uln	Per
10*	**Med**	-	-	-
11*	Rad	**Med 3**, Med, **Med^{F}**, Med^{F}, **Uln 2**, Uln 2, **Rad 2**, **Mus**	Uln	Med
12*	**Uln**	**Med**, Med, Uln	Uln 2	-
13*	Mus	Med^{F}, **Uln**, Uln	-	Per
14*	Med^{F}	Rad	-	-
15*	Uln	-	-	-
16*	Mus	Med^{F}	-	-
17*	Med^{F}	Med, Uln 2	-	Med, Uln, Per 2
18	**Uln**	**Med**, Med^{F}, **Uln 2**, **Rad**, Rad	Uln 2	Uln, Per
19	Med^{F}, **Rad**	**Med**, **Uln**	Med	-
20	Uln	**Med**, **Med^{F}**, Uln	-	Uln
21	Med	**Rad**	-	-
22*	-	**Med 2, Med^{F}**, **Uln 2**, Uln	Med, Uln 2	-
23*	-	**Med**, Med^{F}, **Uln**, Rad	-	-
24*	-	Med^{F}, Uln 3	Uln 2	Tib, Per
25*	-	**Med**, **Uln**	Uln	Med, Per
26*	-	Uln	-	Uln, Tib, Per
27*	-	**Med**	Uln	-
28	-	Med, Uln	-	Med 2
29	-	Med, Uln	-	Med 2
30	-	Uln	-	Per
31	-	Med	-	Med 2, Uln 2, Per
32	-	Med	-	Med
33	-	Med	-	Med
34	-	-	Uln 2	-
35	-	-	-	Med
36	-	-	-	Per
37	-	-	-	Med

** = responder. CB = conduction block. CV = conduction velocity. DML = distal motor latency. Med = median nerve with recording from the m. abductor pollicis brevis. Uln = ulnar nerve. MedF = median nerve with recording from the m. flexor carpi radialis. Rad = radial nerve. Mus = musculocutaneus nerve. Tib = tibial nerve. Per = deep peroneal nerve. Bold = increased temporal dispersion i.e., duration prolongation on proximal versus distal stimulation > 30%. The numbers refer to the number of affected segments when more than one segment is affected.*

Response to treatment and follow-up

Patients 1 - 17 and 22 - 27 responded favourably to IVIg. The age at onset of disease, the number of affected limb regions before treatment and the number of patients with CK > 180 U/L were significantly lower in responders than in non-responders (table 1). Elevated anti-GM1 antibodies were found significantly more often in responders than in non-responders. Although not significant, MR imaging of the brachial plexus was abnormal (see figure 1 of chapter 2) in 10 responders compared with three non-responders. The percentage of segments with definite CB and the mean distal CMAP amplitude were significantly higher in responders. We additionally performed a logistic regression analysis with the variables that showed significant differences between responders and non-responders. In this model the mean number of affected limb regions before treatment followed by the number of patients with an elevated CK were significantly correlated with response to treatment. All responders received IVIg maintenance treatment as was previously published for a smaller group.[225]

At follow-up, the characteristics of the 14 non-responders appeared to be heterogeneous. In five patients (18-21 and 34) the clinical characteristics and course of the disease were similar to that of responders. All five patients had either definite CB (18-21) or abnormal MR imaging scans (18,19 and 34). Four of these patients (18, 20, 21 and 34) had a relatively long disease duration (11, 36, 14 and 11 years). In nine other patients (28-33, 35-37) we found evidence for a more generalized disorder of motor neurons: in seven patients (28-33 and 36) weakness progressed to all four limbs (eight regions); three patients (28,29,35) died of respiratory failure 5, 3 and 4 years after disease onset; two patients (30,31) were on nocturnal ventilation 2 and 3 years after disease onset and patient 36 had a vital capacity of 56% of the predicted value two years after disease onset; patient 37 developed upper motor neuron signs four years after disease onset. In six of these nine patients (28 - 33) probable CB was found on electrophysiological examination and in three of them (35 - 37) only features other than CB compatible with demyelination.

Comparison of electrodiagnostic criteria

When our criteria for CB were applied, all 23 responders had CB; but also 10 non-responders (table 3). We adjusted the criterion for probable CB to identify a maximum number of responders with CB and non-responders without CB, but could not obtain a criterion such that all responders and fewer than 10 non-responders had CB. In one example (probable CB: amplitude reduction of $\geq 40\%$ in an arm nerve) the number of non-responders was reduced from six to zero patients but two responders had no CB (table 3). Therefore, we used our original criteria for CB in the proposed diagnostic criteria for MMN (see below). As our electrodiagnostic

Table 3. Number of patients fulfilling different criteria for conduction block

	Responders N = 23	*Non-responders N = 14*	*p-value*
Criteria present study			
Definite CB	17 (74%)	4 (29%)	
Probable CB	6 (26%)	6 (43%)	
No CB	0 (0%)	4 (29%)	< 0.01
*Criteria adjusted from present study**			
Definite CB	17 (74%)	4 (29%)	
Probable CB	4 (17%)	0 (0%)	
No CB	2 (9%)	10 (71%)	< 0.0001
Criteria Lange31/Katz et al.11			
Definite CB	11 (48%)	2 (14%)	
Probable CB	4 (17%)	1 (7%)	
No CB	8 (35%)	11 (79%)	< 0.05
Criteria AAEM24			
Definite CB	8 (35%)	4 (29%)	
Probable CB	8 (35%)	3 (21%)	
No CB	7 (30%)	7 (50%)	NS

*CB = conduction block. NS = not significant. * = definition definite CB unchanged; probable CB defined as amplitude reduction > 40% in an arm nerve.*

protocol included the nerves for which the American Association of Electrodiagnostic Medicine (AAEM)[162] defined CB and the nerves investigated by Katz et al.[111], we applied their criteria in these nerves of our patients (table 3).

Proposed diagnostic criteria for MMN

Based on the clinical, laboratory and electrodiagnostic features, the response to IVIg, and the follow-up, we propose diagnostic criteria for MMN (table 4). After applying these criteria to our patients, 21 patients had 'definite' MMN (17 responders, 4 non-responders), seven patients 'probable' MMN (5 responders, 2 non-responders) and nine patients 'possible' MMN (1 responder, 8 non-responders). All responders (patients 1-17) and non-responders (patients 18-21) with definite CB fulfilled the clinical and laboratory criteria for definite MMN. Of the six responders with probable CB five (patients 22-25 and 27) had probable MMN and one (patient 26) who had a CSF protein of > 1 g/L possible MMN. Of the six non-responders with probable CB two (patients 29 and 31) had probable MMN and four had possible MMN based on age at onset (>65 years) in patients 32 and 33, the number of affected limb regions (>6) in patient 28, and both age at onset and affected limb regions in patient

Table 4. Proposed diagnostic criteria for MMN

I. Clinical criteria

1. Slowly progressive or stepwise progressive limb weakness
2. Asymmetric limb weakness
3. Number of affected limb regions < 7. Limb regions are defined as upper arm, lower arm, upper leg or lower leg on both sides (max. 8)
4. Decreased or absent tendon reflexes in affected limbs
5. Signs and symptoms are more pronounced in upper than in lower limbs
6. Age at onset of disease: 20 - 65 years
7. No objective sensory abnormalities except for vibration sense
8. No bulbar signs or symptoms
9. No upper motor neuron features
10. No other neuropathies (e.g. diabetic, lead, porphyric or vasculitic neuropathy, chronic inflammatory demyelinating polyneuropathy, Lyme neuroborreliosis, post radiation neuropathy, hereditary neuropathy with liability to pressure palsies, Charcot-Marie-Tooth neuropathies, meningeal carcinomatosis)
11. No myopathy (e.g. facioscapulohumeral muscular dystrophy, inclusion body myositis)

II. Laboratory criteria

1. CSF protein < 1g/L
2. Elevated anti-GM1 antibodies
3. Increased signal intensity on T2 -weighted MR images of the brachial plexus

III. Electrodiagnostic criteria

1. Definite motor CB: CMAP area reduction on proximal versus distal stimulation of at least 50%, over a long segment (between Erb and axilla, upper arm, lower arm, lower leg), or a CMAP amplitude reduction on proximal versus distal stimulation of at least 30% over a short distance (2.5 cm) detected by inching. CMAP amplitude on stimulation of the distal part of the segment with motor CB of at least 1 mV
2. Probable motor CB: CMAP amplitude reduction on proximal versus distal stimulation of at least 30% over a long segment of an arm nerve. CMAP amplitude on stimulation of the distal part of the segment with motor CB of at least 1 mV
3. Slowing of conduction compatible with demyelination: MCV < 75% of the lower limit of normal; DML or shortest F wave latency >130% of the upper limit of normal or absence of F waves all after 16 - 20 stimuli. CMAP amplitude on distal stimulation of at least 0.5 mV.
4. Normal sensory nerve conduction in arm segments with motor CB. Normal SNAP amplitudes on distal stimulation.

Definite MMN:	I 1 - 11	and	II 1	and	III 1 + 4
Probable MMN:	I 1 - 3, 6 -11	and	II 1	and	III 2 + 4
Possible MMN:	I 1, 7 - 11	and	II 2 or 3	or	III 3 + 4

CSF = cerebrospinal fluid. MR = magnetic resonance. CB = conduction block. CMAP = compound muscle action potential. MCV = motor conduction velocity. DML = distal motor latency. SNAP = sensory nerve action potential.

30. All four non-responders with features other than CB compatible with demyelination (patients 34-37) were diagnosed as possible MMN. The likelihood of responding to IVIg treatment was 81% for definite MMN, 71% for probable MMN and 11% for possible MMN.

Discussion

We performed a prospective study on 37 patients, all of whom received a standardized clinical, laboratory and electrophysiological examination, and IVIg treatment. We used loose inclusion criteria consisting of a lower motor neuron syndrome and any feature compatible with demyelination on electrophysiological examination. Based on the clinical, laboratory and electrophysiological characteristics of these 37 patients we propose diagnostic criteria for MMN that have been verified by follow-up and response to IVIg treatment.

The clinical criteria consist of 11 items of which five (7-11) are exclusion items that all patients need to fulfill. All patients in our study developed slowly or stepwise progressive, asymmetric, limb weakness (items 1 and 2). Weakness progressed slowly in a multifocal fashion in 30 patients, and in a more generalized fashion to all limb regions in seven patients. The latter group of patients appeared to be non-responders to IVIg. Therefore we required that the number of affected limb regions had to be less than seven (item 3) for the diagnosis of definite or probable MMN. Using a logistic regression model the mean number of affected regions before treatment was significantly correlated with response to IVIg treatment. At the time of inclusion, all patients in our study had decreased or absent tendon reflexes in affected limbs (item 4). One non-responder developed hyperreflexia in wasted arm muscles during follow-up. A majority of MMN patients had more pronounced symptoms in the upper limbs than in the lower limbs (item 5): even in the 15 patients with lower limb onset, at a later stage the arms were more affected than the legs. The age at onset ranged from 20 to 64 years in previous studies of well-defined patients with MMN who responded to IVIg[8,9,28,34,111,128,155,225] which is similar to our study (range 20-58 years). In contrast, chronic inflammatory demyelinating polyneuropathy (CIDP) can start in any decade of life[54], and MND at an older age. For these reasons, we included a range of 20-65 years for the age at onset of definite or probable MMN in our proposed diagnostic criteria (item 6). This item is further supported by our study, as non-responders had a significantly higher age at disease onset than responders.

The laboratory criteria consist of three items. A CSF protein of < 1g/L (item 1) is required for the diagnosis of definite and probable MMN in our proposed criteria as this was found in all patients previously reported as well as in all except one patient in our study. A higher CSF protein may point to CIDP or infiltration of malignant cells in nerve roots. Elevated anti-GM1 antibodies (item 2) are found in 20%[123,212] to 80%[116,175] of the patients with MMN. In our laboratory, approximately one-third of the patients with MMN and 5-10% of the patients with LMND have IgM anti-GM1 antibody titers higher than normal and disease controls.[223,228] In the present

study we found elevated anti-GM1 antibodies only in responders. However, other studies have shown that just the presence of anti-GM1 antibodies does not identify a subgroup of patients who respond to IVIg[223] or immunosuppressive treatment.[211,221] We included in our diagnostic criteria that patients with elevated anti-GM1 antibodies are diagnosed as possible MMN. Abnormal MR imaging of the brachial plexus (item 3) may also support the diagnosis of MMN. We previously reported increased signal intensities on T2-weighted MR images of the brachial plexus, sometimes associated with a diffuse nerve swelling, in patients with MMN, CIDP or multifocal inflammatory demyelinating neuropathy.[232,237] In contrast, brachial plexus MR images of progressive spinal muscular atrophy patients and of the clinically nonaffected sides in MMN patients were normal. These findings strongly suggest that these MR imaging abnormalities represent demyelination. In the present study, 10 of 21 responders had an abnormal MR imaging scan of the brachial plexus, but also three of 10 non-responders. However, two of these three non-responders fulfilled the clinical criteria for definite MMN.

The electrodiagnostic criteria consist of one exclusion item (normal sensory nerve conduction (item 4)), and three items characterizing demyelination (definite CB, probable CB or features other than CB compatible with demyelination (items 1-3)). Criteria for CB require a CMAP reduction P/D exceeding the CMAP reduction P/D caused by increased temporal dispersion in demyelinating disorders or polyphasic motor-unit potentials (MUPs) in axonal degeneration.[37] Our criterion for definite CB (area reduction P/D at least 50%) is based on the finding that computer simulation of temporal dispersion of biphasic MUPs yields an area reduction P/D of no more than 50%.[181] With more polyphasic MUPs, the CMAP reduction P/D is possibly greater.[162] Therefore many studies require that temporal dispersion, as measured by duration prolongation P/D, has to be limited.[111,123,162] We did not include this in our criteria, because temporal dispersion was reduced by warming.[189] Warming for at least 30 min in water at 37° C yields a nerve temperature close to 37° C[67,70] and improves the detection of CB by reducing temporal dispersion[68,189] and inducing CB in demyelinating neuropathy[68,180] but not in axonal neuropathy.[65] To minimize underdiagnosis of mild CB we defined a criterion for probable CB, i.e. amplitude reduction P/D of at least 30% in an arm nerve.[2,160]

We compared our standardized electrodiagnostic protocol and criteria for CB with those of Katz et al. and the AAEM (table 3).[111,162] When the criteria of Katz et al.[111] were applied to those nerves of our patients that were included in their protocol no CB was found in eight responders (table 3), confirming their conclusion that diagnostic criteria requiring CB may lead to underdiagnosis of MMN. However, with our criteria more segments with CB were found in responders. These differences can be explained by several factors. First of all, as we did not require limited tempo-

ral dispersion, more nerve segments fulfilled our criteria for CB. After exclusion of segments with increased temporal dispersion (duration prolongation P/D > 30%)[123,160], five patients (4 responders and 1 non-responder) no longer fulfilled the criteria for definite CB. Furthermore, four responders no longer had CB but only features other than CB compatible with demyelination and one responder no features of demyelination at all, indicating that criteria requiring limited temporal dispersion may lead to underdiagnosis of a treatable neuropathy. On the other hand, our requirement that the distal CMAP has to be at least 1mV for the diagnosis of CB, is stricter than in the criteria of the AAEM (distal CMAP amplitude of at least 20% of the lower limit of normal) or Katz et al. (no requirement). Secondly, our protocol was more extensive as it was performed bilaterally and included the musculocutaneous nerve and the median nerve with recording from the flexor carpi radialis muscle. Neither was included in the AAEM criteria and the latter was not investigated by Katz et al.. Four responders had definite CB in one of these nerves only (table 2). Thirdly, warming of the limbs yields more segments with CB.[68,180]
Of the 10 non-responders with CB, four had definite CB and six probable CB (table 3). All four patients with definite CB fulfilled the clinical criteria for definite MMN, also during follow-up, and two of them had an abnormal MR imaging scan suggestive of demyelination. A possible explanation for the failure of IVIg treatment in these patients may be extinction of the immune process or extensive axonal degeneration, which is supported by a lower mean distal amplitude in the non-responders than in the responders with definite CB. Both may be the result of a longer disease duration in the non-responders. Of the six non-responders with probable CB, two fulfilled the diagnostic criteria for probable MMN and four those of possible MMN due to clinical criteria (age at onset >65 years and >6 affected limb regions). It is likely that in these patients the finding of probable CB was caused by phase cancellation of polyphasic MUPs rather than true CB or increased temporal dispersion. In these six patients, as well as in two other non-responders, we found evidence for a more generalized disorder of motor neurons (progressive weakness to all limb regions, respiratory failure) at follow-up, such that these patients were diagnosed as having LMND or progressive spinal muscular atrophy.[25,30,158] One non-responder developed upper motor neuron signs and the diagnosis was changed to probable amyotrophic lateral sclerosis according to the revised El Escorial criteria.
We propose a set of diagnostic criteria, which combines clinical, laboratory and electrodiagnostic features of MMN, that may help to predict whether patients respond to treatment. These criteria may be useful in clinical practice as well as in clinical trials.

Multifocal inflammatory demyelinating neuropathy: a distinct clinical entity?

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Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a sensorimotor neuropathy which is characterized by a relapsing or progressive course and a beneficial response to immunological treatment.[11,54] In typical cases there is symmetrical weakness with sensory impairment in arms and legs, both distally and proximally. On electrophysiological examination symmetrical features of demyelination have been found.

Multifocal motor neuropathy (MMN) differs from CIDP in the presence of asymmetrical weakness without sensory loss, more often in the arms than in the legs.[170,176] Electrophysiological examination in MMN shows multifocal motor conduction block. MMN responds to treatment with intravenous immunoglobulins (IVIg) and cyclophosphamide but, contrary to CIDP, usually not to prednisone.

In previous studies several patients have been described who have an asymmetric sensory or sensorimotor demyelinating neuropathy which has several features in common with CIDP or MMN, but who do not exactly fulfill the diagnostic criteria for these diseases. To help distinguish this neuropathy from CIDP and MMN, we present clinical, electrophysiological, radiological and pathological features of six patients and a literature review. We propose calling this neuropathy 'multifocal inflammatory demyelinating neuropathy' (MIDN).

Methods

Patients

Six patients were included on the basis of an asymmetrical sensory or sensorimotor polyneuropathy and demyelinating features found on electrophysiological examination. Extensive clinical and laboratory evaluation excluded other causes for neuropathy. Muscle strength was measured in all patients, using the Medical Research Council scale (MRC).[142] In patients 1, 2, 4 and 5 muscle strength was also measured in Newton (N), using a hand-held dynamometer, in the following muscle groups: flexors and extensors of the elbow, wrist, hip, knees and feet; shoulder abductors, hand grip. In patient 3, hand grip was measured using a Jamar meter. In patient 6 who had a predominantly sensory polyneuropathy, sensory loss was measured using a vibrameter type 3 (Somedic AB, Stockholm, Sweden)[71] and ataxia was quantified by a tapping test.[159] IgM and IgG anti-GM1 antibodies were measured as described previously.[228]

Electrophysiological studies

Electrophysiological studies were performed after warming the arms and legs in water at 37°C for 30 minutes.[67] All patients were investigated on both sides. Nerve conduction studies were performed using surface electrodes. Motor nerve conduction was investigated in the median, ulnar, radial, musculocutaneus, deep peroneal and tibial nerves, but not in the radial and musculocutaneous nerves of patients 1, 3 and 5. The compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis, flexor carpi radialis, abductor digiti minimi, extensor carpi ulnaris, biceps brachii, extensor digitorum brevis, and abductor hallucis muscles. Stimulation sites included: wrist, 5 cm below the elbow, 5 cm above the elbow, axilla, Erb's point, ankle, 5 cm below the fibular head, and popliteal fossa. F waves were recorded following 20 stimuli, applied to the median, ulnar, deep peroneal and the tibial nerves at the wrist or the ankle. From each CMAP, the amplitude, area and duration of the negative part were determined. For each nerve segment the reduction in CMAP amplitude or CMAP area on proximal versus distal stimulation was calculated as: (distal CMAP minus proximal CMAP) 100% / distal CMAP. The increase in CMAP duration was calculated as: (proximal CMAP minus distal CMAP) 100% / distal CMAP. Definite conduction block was defined as a reduction in CMAP area of at least 50%[68,181] and probable conduction block as a reduction in CMAP amplitude of at least 30% in an arm nerve.[2,66] Increased temporal dispersion was defined as an increase in CMAP duration of at least 30%.[123] Conduction block or increased temporal dispersion was only considered when the CMAP amplitude on distal stimulation exceeded 1 mV. Evidence of demyelination included: decreased motor nerve conduction velocity or increased distal motor nerve latency or increased minimal F wave latency, according to previously described criteria for demyelination[36] and absence of F waves. Sensory nerve conduction on distal stimulation was investigated in the median, ulnar, radial and sural nerves; the amplitude of the negative part of the sensory nerve action potential (SNAP) was determined.

Magnetic resonance imaging of the brachial plexus

The patients were scanned according to a protocol designed for magnetic resonance (MR) imaging of the brachial plexus as described previously.[237] The standard protocol included sagittal proton-density and T2-weighted spin-echo images (TR-1800 msec, TE-30 and 90 msec, NSA-2, slice thickness 6 mm, gap 4 mm) from the spinal cord to the medial side of the humeral head on both sides. In the coronal plane, thin T1-weighted spin-echo images (TR-600-700 msec, TE-20 msec, NSA-4, slice thickness 3 mm, gap 0.3 mm) and a fat-suppressed T2-weighted fast-spin-echo (FSE) sequence (IR-FSE, TR-3103 msec, TE-100 msec, TI-150 msec, echo train length 11, NSA-4, slice thickness 3 mm, gap 0.3 mm) were performed on both

sides. In patient 2 a coronal gradient echo sequence (TR-550 msec, TE-14 msec, flip angle -20) was carried out instead of the fat-suppressed T2-weighted FSE sequence. Gadolineum-DTPA was administered in patients 1, 2 and 6.

Results

Patients

Patient characteristics are listed in table 1. The age at disease onset ranged from 28 to 58 years; and disease duration from 6 to 18 years. The first symptoms were sensory in patients 2, 4 and 6, sensorimotor in patient 3 and motor in patients 1 and 5. The initial symptoms occurred in one arm in patients 1, 2, 3, 4 and 6 and in one leg in patient 5. During the course of the disease the neurological deficit progressed to other limbs but remained asymmetrical in patients 2, 4, 5 and 6. After 6 and 8 years of follow-up still only one limb was affected in patients 1 and 3. The disease course was relapsing-remitting in patients 1, 2, 4 and 5, at least for a substantial part of the disease history, and progressive in patients 3 and 6. The cerebral spinal fluid (CSF) protein levels were normal or only mildly raised in all patients (range 44 - 82 mg/dl). Anti-GM1 antibodies were measured in serum of patients 1, 2, 3 and 6, and were not elevated. Patients 3 and 5 were treated with corticosteroids which resulted in deterioration. Patient 3 also received cyclophosphamide without effect. All patients showed a benificial response to IVIg treatment.

Electrophysiological studies

The electrophysiological findings are summarized in table 1. In all patients the nerve conduction abnormalities were asymmetrical. Conduction block was found in all patients (definite in patients 1,3, 4 and 5 and probable in patients 2 and 6). Evidence of demyelination other than conduction block was found in patients 1, 2, 4, 5 and 6. Decreased CMAPs were found in patients 1, 2, 3, 4 and 5 who currently have motor symptoms. Decreased distal SNAP amplitudes were found in all patients. In

Table 1. RA= right arm, LA= left arm, RL= right leg, LL= left leg. N III = right third cranial nerve. ↑ = increased. ↓ = decreased. - = not investigated.= biopsy material was also taken from the ramus superficialis of the left radial nerve; this showed a normal aspect. CV = conduction velocity. CMAP= compound muscle action potential. SNAP= sensory nerve action potential. Med= median nerve. Uln= ulnar nerve. Rad = radial nerve. Mus= musculocutaneous nerve. Tib= tibial nerve. Per= peroneal nerve. The nerve segments are labeled by superscript: L= lower arm or lower leg, U= upper arm, S= shoulder (i.e. between axilla and Erb's point).*

Table 1. Clinical features, laboratory investigations and electrophysiological findings in six patients

		Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*
Clinical features							
Sex		male	female	male	male	male	male
Age at onset (years)		37	33	58	28	29	41
Duration of disease (years)		6	6	8	7	18	8
Site of onset		left hand	left arm	right hand	right hand	right leg	right hand
Currently affected site(s)		LA	RA, LA	RA	RA, LA, LL	RA, RL, LL and N. III	RA, LA, RL, LL
First symptoms		motor	sensory	sensorimotor	sensory	motor	sensory
Current symptoms		sensorimotor	sensorimotor	sensorimotor	sensorimotor	sensorimotor	sensory
Disease course		relapsing/remitting	relapsing/remitting	progressive	relapsing/remitting	relapsing/remitting	progressive
Atrophy		yes	yes	no	yes	no	no
Reflexes		↓ in RA	↓ in RA, absent in LA	absent in RA	absent	absent in RA, LA, RL	absent in RA, LA, LL
Painful and thickened nerve		no	yes	no	no	no	no
Laboratory investigations							
CSF protein (mg/dl)		44	66	<50	48	82	54
Anti-GM1 antibodies		no	no	no	-	-	no
↓ signal intensity on MRI of brachial plexus		LA>RA	LA (1996), LA=RA (1998)	-	absent	LA=RA	RA>LA
Pathology sural nerve		normal	-	-	normal*	signs of de- /remyelination	normal
brachial plexus		-	inflammatory signs	-	-	-	-
Electrophysiological findings							
Definite conduction block	Left	Med ^{L}, Uln ^{L}, Uln ^{U}			Med ^{L}, Tib ^{L}	Uln ^{S}	
	Right	Med ^{L}, Uln ^{L}		Med ^{L}, Uln ^{U}		Med ^{S}, Uln ^{S}	
Probable conduction block and/or ↑ temporal dispersion	Left	Med ^{L}, Uln ^{L}	Med ^{S}				
	Right	Uln ^{L}				Med ^{U}	Rad ^{S}
CV in demyelinating range	Left	Med ^{L}, Med ^{U}, Uln ^{L} , Uln ^{U}	Mus		Med ^{S}	Uln ^{S}, Tib ^{L}	
	Right	Per ^{L}	Mus			Uln ^{U}, Uln ^{S}	Med ^{S}, Mus ^{S}
↓ distal CMAP amplitude	Left			Per	Per	Per, Tib	
	Right	Per	Med, Uln			Per, Tib	
↓ distal SNAP amplitude	Left	Med, Rad		Sur	Rad	Med, Rad	Sur
	Right		Med	Med, Uln, Sur		Med, Uln, Rad	Med, Uln

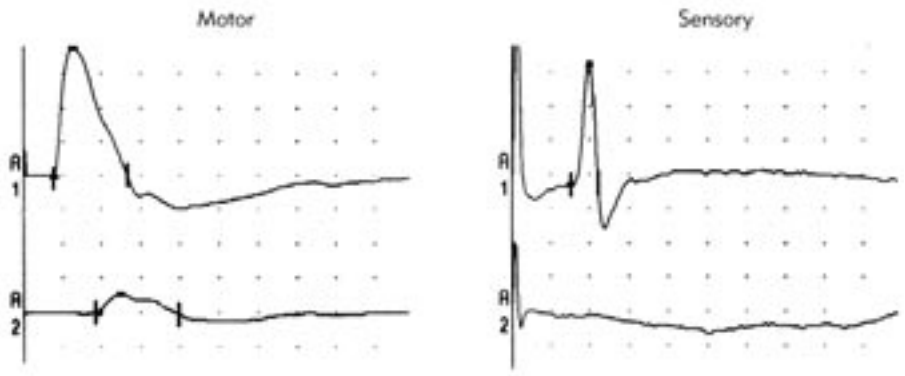
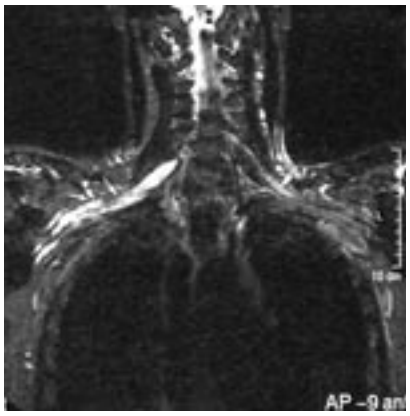


Figure 1. Left median nerve conduction studies in patient 4. A1: stimulation at the wrist. A2: stimulation at the elbow. Left half of figure: motor conduction, time base 5 ms/division, sensitivity 2 mV/division. There is severe reduction of the CMAP on elbow versus wrist stimulation, indicating partial motor conduction block. Right half of the figure: sensory conduction, time base 2 ms/division, sensitivity 10 µV/division. The SNAP on wrist stimulation is normal, whereas the SNAP on elbow stimulation is absent, indicating conduction block or severe temporal dispersion in sensory nerve fibers. Motor and sensory conduction in the right median nerve were normal.

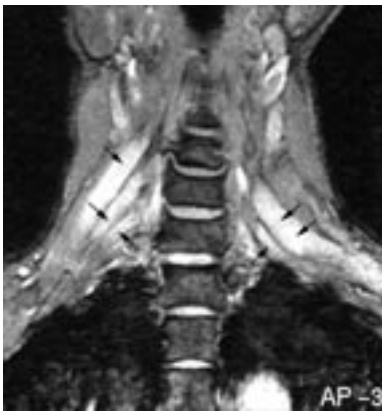
patient 4 definite motor conduction block was found in the lower arm segment of the left median nerve (figure 1). In the same nerve, the SNAP on wrist stimulation was normal, whereas that on elbow stimulation was absent. In the right median nerve, SNAPs on wrist and elbow stimulation were normal. These findings indicate conduction block or severely increased temporal dispersion in sensory fibers of the lower arm segment of the left median nerve. Conduction block in sensory nerve fibers is difficult to determine because, even in a normal nerve, the SNAP amplitude is smaller on distal than on proximal stimulation. This is due to phase cancellation of desynchronized action potentials in sensory nerve fibers.[163]

Magnetic resonance imaging of the brachial plexus

MR imaging of the brachial plexus was done in all patients except patient 3. In patients 1, 2, 5 and 6 T2-weighted images showed a swollen brachial plexus with increased signal intensities (figure 2). The distribution of the MR imaging abnormalities corresponded with the distribution of symptoms in patients 1, 2, 5 and 6. In patients 1 and 6 the MR imaging abnormalities were more pronounced on the side that was clinically more affected. In patient 2, MR-imaging in 1996 showed a swollen brachial plexus on the left side; two years later, when the right upper limb was also affected, abnormalities were found on both sides. In patient 5 the abnor-



2.1



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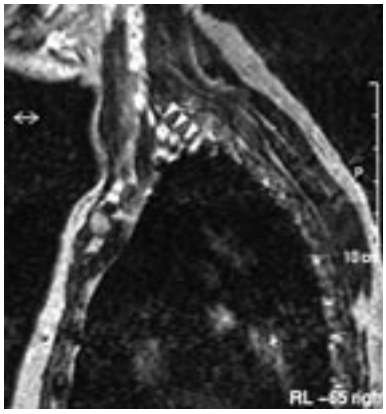

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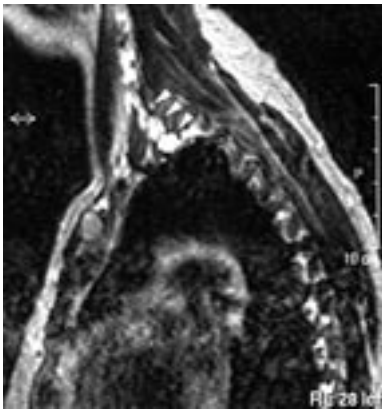

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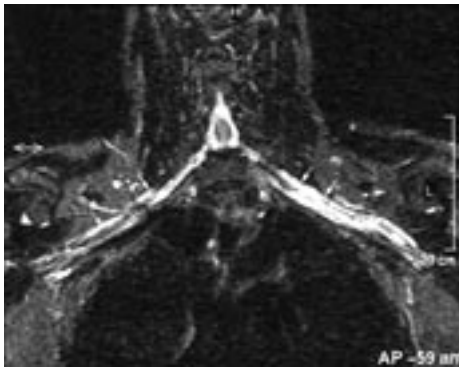

2.5

Figure 2. Arrows indicate swellings and increased signal intensities in the brachial plexus.
2.1 Coronal fat-suppressed T2-weighted FSE sequence of the brachial plexus of patient 1; the abnormalities are more pronounced on the right than on the left side. 2.2 Coronal FFE sequence of the brachial plexus of patient 2, showing swollen brachial plexus on both sides. 2.3 Sagittal T2-weighted MR image of the brachial plexus of patient 6 on the right, and 2.4 on the left side, showing swollen brachial plexus with increased signal intensity greater on the left than on the right side. 2.5 Coronal fat-suppressed T2-weighted FSE sequence of the brachial plexus of patient 6; the abnormalities are more pronounced on the left than on the right side.

malities were symmetrical. In patient 4 no abnormalities of the brachial plexus were detected by MR imaging. There was no enhancement following the administration of gadolineum-DTPA.

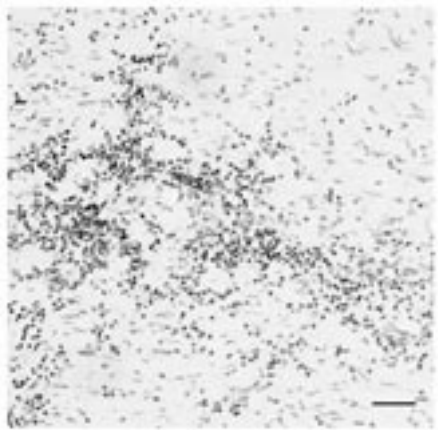

Figure 3. Lymphocytic infiltrates in endoneurial space of brachial plexus of patient 2. Hematoxylin and Eosin staining. Bar = 50 μ.

Pathology

Sural nerve biopsies were normal in patients 1, 4 and 6. In patient 5 the sural nerve biopsy supported the diagnosis of demyelinating neuropathy: myelinated fiber density was mildly reduced to 5514/ mm^2, signs of de- and remyelination were found, including scattered onion bulbs, macrophages and some T-lymphocytes. Teased fibers were normal. In patient 2 the biopsy specimen of the brachial plexus showed prominent infiltrates of mainly T- and some B-lymphocytes and macrophages (figure 3)

Discussion

The six patients in our study presented with a sensory or sensorimotor neuropathy affecting only one limb. In four patients the neuropathy progressed in an asymmetrical fashion to other limbs over a period of years. The multifocal nature of the clinical presentation was confirmed by electrophysiological examination which showed evidence of multifocal demyelination and conduction block in motor and sensory nerves. MR imaging of the brachial plexus revealed swollen nerves and increased signal intensities on T2-weighted imaging. These abnormalities are also observed in patients with CIDP and MMN and are suggestive of inflammation.[237] A biopsy taken from the brachial plexus in one patient indicated an inflammatory process. Further evidence of an immune mediated neuropathy in these patients was the beneficial response to immunological treatment.

The neuropathy in our patients does not fulfill the diagnostic criteria for CIDP that are proposed by Barohn et al.[11] and Dyck et al.[54] as the distribution of weakness or sensory loss is not symmetrical. In the 1991 research criteria for CIDP proposed by the American Academy of Neurology (AAN)[36], 'dysfunction of more than one limb of a peripheral nerve nature' is required for a diagnosis of CIDP. This was not true

for our patients, at least not during a substantial period of their disease course. Additionally, only one of the six patients fulfilled the electrophysiological criteria of the American Academy of Neurology for the diagnosis CIDP. Although mild sensory abnormalities on clinical, electrophysiological and pathological examination are described in MMN[155,170] the prominent sensory abnormalities that were found in our six patients on clinical and electrophysiological examination (including 'sensory conduction block'), make a diagnosis of MMN unlikely. Also, the disease course was relapsing/remitting in four patients and anti-GM1 antibodies were negative in all patients both of which are unusual for MMN.

In the literature, we identified 34 additional patients with a similar asymmetrical demyelinating neuropathy, described under various names.[1,4,39,130,147,148,193,216,240] The first description of a multifocal demyelinating sensorimotor neuropathy was by Lewis and Sumner et al.[130] In these cases there was electrophysiological evidence of multifocal persistent motor conduction block which later became the hallmark of MMN. Confusingly, Lewis' patients have been considered to represent the first described patients of MMN, although their clinical and electrophysiolgical features indicate that they belong to the group of patients that is discussed here. Of the 40 patients (34 in the literature and our six patients) the upper extremities were initially affected in 31 patients (78%), and the lower extremities in nine patients (22%). In 11 patients (35%) with upper limb neuropathy, the disease eventually progressed to the lower limbs. This shows that the neurological deficit was not limited to the upper limbs in many patients as was suggested previously.[216] Moreover, the neuropathy was multifocal rather than focal, a term used in two other studies.[216,240] The disease course was relapsing in 11 patients (28%) and progressive in 19 (47%), which is comparable to CIDP.[11,54] The disease course was unknown in 10 patients (25%).[193] Cranial nerve involvement was present in seven patients (18%), including our patient 5.[1,130,147,193] Cranial nerve signs are not common in CIDP[11,18,54] and have been described in only one patient with MMN[107], but may be helpful to diagnose an inflammatory demyelinating neuropathy if other diagnoses are still being considered (see below). The CSF protein level was normal or only mildly elevated (< 100 mg/dl) in 29 of the 31 patients (94%) analysed, which is comparable to MMN, whereas in CIDP 50 per cent of patients have CSF protein levels in excess of 100 mg/dl.[18] Saperstein et al. recently found that the CSF protein level in their 11 patients with an asymmetric demyelinating neuropathy was more frequently elevated (>50 mg/dl) than in MMN, which they considered a feature similar to CIDP.[193] However, the range of CSF protein in their patients (32-84 mg/dl) is similar to that of patients with MMN previously published and to our six patients presented here (44-82 mg/dl). In contrast to MMN, anti-GM1 antibodies were negative in all 19 patients (48%) with an asymmetric demyelinating neuropathy who were tested. MR

Table 2. Comparison of general features of MMN, CIDP and MIDN

	CIDP	*MMN*	*MIDN*
Symptoms			
Distribution	Symmetrical	Asymmetrical	Asymmetrical
Arms > legs	No	Yes	Yes
Prominent sensory symptoms	Yes	No	Yes
Generalized areflexia	Yes	No	Rare
Disease course			
Progressive	Yes	Yes	Yes
Relapsing	Yes	Rare	Yes
Laboratory features			
CSF protein > 100 mg/dl	Yes	No	Rare
Anti-GM1 antibodies	Rare	30-50% of patients	No
Abnormal MR-imaging of brachial plexus	Symmetrical	Asymmetrical*	Asymmetrical*
Response to treatment			
Intravenous immunoglobulins	Yes	Yes	Yes
Corticosteroids	Yes	No**	Yes**

**= corresponding with neurological deficit. **= deterioration may occur.*

imaging of the brachial plexus was performed in 10 patients (25%): it showed a normal aspect in five patients, asymmetrical increased signal intensities corresponding with the clinical signs and symptoms in three patients, and symmetrical bilateral increased signal intensities in two patients.

That these patients can be confusing diagnostically, becomes evident when the initial diagnoses are reviewed that were made in some of the 40 patients. Neuralgic amyotrophy was diagnosed in three of the 40 patients (8%), including our patient 6, in whom pain was a prominent symptom[4,39] and neurofibroma or Schwannoma in nine patients (23%), including our patient 2. Interestingly all these nine patients had a supraclavicular or popliteal palpable mass.[39,148,216] Focal hypertrophic changes of a plexus, nerve trunk or nerve, as seen in CIDP[53,137] can mimic a nerve sheath tumor such as neurofibroma, Schwannoma or perineurioma. In these cases, the finding of prominent lymphocytic infiltrates in nerve tissue can differentiate inflammatory from non-inflammatory causes. Other mimicking syndromes were median nerve mononeuropathy in two patients[216,240] (5%) and radiculopathy in our patient 5 who had mononeuropathic lower limb weakness.

Several treatment strategies have been used in patients with an asymmetrical demyelinating neuropathy. Treatment with IVIg resulted in a beneficial response in all of our patients and in 11 patients described by others.[193,216] Although one patient described previously[216] and two of our patients deteriorated after treatment with

corticosteroids, which has also been reported in patients with MMN or pure motor CIDP[50,227], a beneficial response to corticosteroids has been reported in 14 out of 20 treated patients.
We propose to name the disease in these patients 'multifocal inflammatory demyelinating neuropathy' (MIDN), as it has features in common with both CIDP and MMN. Major similarities and differences between MIDN, CIDP and MMN are presented in table 2. It is important to separate MIDN from CIDP and MMN in order to facilitate early diagnosis and treatment in patients presenting with an asymmetric sensory or sensorimotor demyelinating neuropathy. Whether MIDN represents a distinct disease entity or is a variant of CIDP cannot be determined until more is known about its pathogenesis. We believe that it is important to recognize MIDN as a distinct clinical entity.

Selected case reports

Patient 1
In 1992 a 37-year-old man complained of diminished sensation in the fingers of his left hand and occasional cramps while writing. The symptoms disappeared after a few months. From 1996, he developed a gradually progressive weakness and numbness in the left hand. He also noticed cramps, fasciculations and stiffness in the leg muscles.
Neurological examination in 1998 revealed wasting and weakness of the left lower arm (forearm flexors and extensors MRC grade 4) and intrinsic hand muscles. Both pinprick and light touch were impaired distally in the left arm. In the lower extremities only a mild weakness of the right foot dorsiflexors (MRC 5-) was found.
In April 1998 he received one course of intravenous immunoglobulins (IVIg) (0.4 g/kg for 5 consecutive days). Muscle strength in the left arm returned to almost normal (elbow extensors from 58 to 84 N, wrist flexors from 78 to 132 N, wrist extensors from 44 to 154 N and grip strength from 24 to 81 N). Sensation improved in the left hand, and muscle stiffness in the legs disappeared. Eight weeks after IVIg treatment the patient deteriorated gradually to pretreatment level. After 10 weeks the patient received a second IVIg course with similar results. Since then he has been on IVIg maintenance treatment of 0.4 g/kg per month.

Patient 2
In 1992 a 33-year-old woman experienced feelings of numbness, tingling and pain in the left upper arm and first three fingers. She had noticed a painful swelling on the left side of her neck. Since 1996 she has had feelings of numbness and tingling in

the fourth and fifth fingers of the right hand and weakness in the right arm fluctuating in intensity over a period of weeks. The symptoms interfered with her work as a restaurant owner.

Neurological examination in 1997 revealed wasting and weakness of shoulder abductors (MRC 2 right, MRC 3 left), both arm flexors (MRC 4), and right intrinsic hand muscles (MRC 4). There was impairment of pinprick and light touch sensation over the radial part of the right forearm, the right fourth and fifth fingers and the lateral part of the left upper arm and the radial part of the left forearm. Because of the painful and palpable swelling at first the diagnosis of Schwannoma was considered. When similar signs and symptoms developed subsequently on the contralateral side and MR-imaging showed an increased signal intensity on that side, neurofibromatosis was considered. On the basis of the biopsy material a diagnosis of inflammatory neuropathy was eventually reached.

After treatment with IVIg (0.4 g/kg for 5 consecutive days) there was clear improvement in sensation as well as muscle strength (left shoulder abductors from 33 N to 88 N; right and left elbow flexors from 48 to 63 N and from 34 to 99 N; right and left grip strength from 26 to 66 N and from 63 to 80 N) lasting until 40 weeks after treatment. Thereafter especially the sensory symptoms gradually worsened and a new IVIg course was given, 48 weeks after the first one.

Demyelination and axonal loss in multifocal motor neuropathy: distribution and relation to weakness

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GH Wieneke, JHJ Wokke, H Franssen

Brain 2002. In press.

Introduction

Multifocal motor neuropathy (MMN) is characterized by slowly progressive, asymmetrical weakness of the limbs without sensory loss.[154] As MMN has proven to be a treatable disorder[8,9,23,24,34,62,107,131,132,146,155] , differentiation from motor neuron disease has become increasingly important.[49] The diagnosis of MMN is based on clinical, laboratory and electrophysiological characteristics.[92,154,171]

Weakness in MMN has been attributed to the consequences of demyelination and axonal loss in peripheral nerves.[61,111] On electrophysiological examination, features of demyelination that can be observed in MMN include conduction block, increased temporal dispersion and severe conduction slowing; the features of axonal loss include needle electromyography abnormalities and decreased distal compound muscle action potentials although the latter can also be caused by distal conduction block.[23,99,109,111,153,213,231] Of these features, conduction slowing compatible with demyelination and increased temporal dispersion are not assumed to give rise to weakness, whereas conduction block and axonal loss are.[61] This assumption has, however, not yet been proven in patients with MMN.

Weakness in MMN usually follows a typical pattern being more prominent in distal than proximal muscles and more prominent in the arms than the legs[111,213], but the mechanisms that lead to this distribution have not yet been elucidated. Explanations for the distribution of weakness in the arms include preferential location of demyelination in nerve segments of the lower arm, preferential location of demyelination in nerve fibres innervating lower arm muscles at the level of the proximal forearm or brachial plexus, or a random distribution of demyelination, resulting in more damage to the longest arm nerves. Insight into these distributions may help one to understand the pathophysiological mechanisms involved in MMN and in fibre length dependency of abnormalities in immune-mediated neuropathies.

Due to the multifocal nature of MMN, one may have to perform an extensive electrophysiological examination in order to detect conduction block or other features of demyelination. Its detection in MMN depends on the criteria used for conduction block and the number of nerves investigated.[58,231] In our extensive electrodiagnostic protocol we investigated a large number of nerves independently from the distribution of weakness while other protocols depend on the investigation of nerves that innervate weak, non-atrophic muscles.[58,111,213] The distribution of electrophysiological abnormalities and the correlation with weak muscle groups in MMN may therefore also have important implications for the way in which the electrodiagnostic investigation is conducted in a patient suspected of having MMN.

The aim of the present study was to assess: (1) whether electrophysiological abnormalities have a preferential or random distribution, (2) whether electrophysiological

abnormalities in a nerve correlate with weakness in the innervated muscles, and (3) whether these results are relevant for the development of optimal electrodiagnostic protocols. For this purpose, we compared the pattern of weakness and electrophysiological abnormalities in 39 patients with multifocal motor neuropathy.

Patients and methods

Patients

Included in the study were 39 patients who were selected from a group of patients with the clinical presentation of an asymmetric lower motor neuron syndrome on the basis of a favourable response to high-dose intravenous immunoglobulins (IVIg).[92,231] On follow-up the response to treatment lasted at least 12 months. The clinical and laboratory features are summarized in table 1. Sensory conduction studies were normal in all patients. The clinical and electrophysiological data were

Table 1. Clinical and laboratory features of 39 patients

Clinical features	
Male sex (n(%))	32 (82)
Age at onset (median; range (yrs))	36.0; 20 - 58
Disease duration (median; range (yrs))	11.0; 2.0 - 27.0
Upper limb onset (n(%))	22 (55)
MRC-sumscore (median; range)[1]	111; 84 - 118
Laboratory features	
CSF protein (g/L)[2] (median; range)	0.46; 0.20 - 1.23
Elevated anti-GM1 antibodies[3] (n(%))	9 (27)
Abnormal MR imaging brachial plexus[4] (n(%))	13 (37)

SD = standard deviation. CSF = cerebrospinal fluid. [1] = Maximum score 120. [2] = investigated in 23 patients. [3] = investigated in 33 patients. Abnormal MR imaging plexus brachialis = swelling and/or increased signal intensity. [4] = investigated in 35 patients.

obtained before IVIg treatment was started. Muscle strength was bilaterally assessed by one investigator (RM Van den Berg-Vos), who was blinded to the results of electrophysiological studies. MRC grading[142] was performed in thenar abductors, hypothenar abductors, wrist extensors, wrist flexors, elbow extensors, elbow flexors, arm abductors, ankle dorsiflexors, ankle plantarflexors, knee extensors, knee flexors, and hip flexors. Weakness was defined as an MRC score < 5. By summing all MRC

grades, a MRC sumscore was calculated for each patient (maximum 120). Most patients were tested for serum IgM anti-GM1 antibodies.[228] Magnetic resonance imaging (MRI) of the brachial plexus was performed according to a protocol described previously.[237]

Electrophysiological studies

Nerve conduction was studied bilaterally by the same investigator (H Franssen), who was blinded to the results of muscle strength measurement. A standardized protocol and surface electrodes were used.[225] Motor nerve conduction was investigated up to Erb's point in the median (recording m. abductor pollicis brevis and m. flexor carpi radialis), ulnar (recording m. abductor digiti V), radial (recording m. extensor carpi ulnaris), and musculocutaneous (recording m. biceps brachii) nerves and up to the popliteal fossa in the deep peroneal (recording m. extensor digitorum brevis) and tibial (recording m. abductor hallucis) nerves. Antidromic sensory conduction was investigated in the median, ulnar, radial and sural nerves. In the case of motor conduction block in the ulnar or median nerve, sensory conduction was measured over the affected segment. F waves were recorded after 20 distal stimuli to the median, ulnar, deep peroneal and tibial nerves. Prior to an investigation, the arms and legs were warmed in water at 37 °C for at least 30 minutes; thereafter they were kept warm by infrared heaters.[67]

For each compound muscle action potential (CMAP) we measured the latency, amplitude, area and duration of the negative part. The following variables were studied: (1) distal amplitude (mV) which is the CMAP amplitude on stimulation of the most distal site of the nerve, (2) amplitude reduction or area reduction (%) on proximal versus distal stimulation (P/D)[232] calculated as (distal CMAP - proximal CMAP x 100) / (distal CMAP), (3) duration prolongation P/D (%) calculated as (proximal CMAP - distal CMAP x 100) / (distal CMAP), (4) motor conduction velocity (MCV), (5) distal motor latency (DML), (6) shortest F-M latency.

Conduction abnormalities were categorized into: (1) definite conduction block (CB) (area reduction P/D ≥ 50% in a long segment, which is lower arm, upper arm, shoulder or lower leg, or amplitude reduction P/D ≥ 30% over 2.5 cm)[66,181,231] , (2) probable CB (amplitude reduction P/D ≥ 30% in a long segment of an arm nerve)[2,160] , (3) increased temporal dispersion (TD) (duration prolongation P/D ≥ 30% in a long segment)[123,160] , (4) conduction slowing compatible with demyelination (MCV decreased below 75% of the lower limit of normal; DML or shortest F-M latency increased above 130% of the upper limit of normal)[66,231] , (5) F-wave absence, (6) decreased distal CMAP (distal CMAP amplitude decreased below the lower limit of normal). The distal CMAP amplitude had to be at least 1.0 mV to score CB and increased TD, and at least 0.5 mV to score conduction slowing com-

patible with demyelination and F-wave absence. Reference values for DML compatible with demyelination in the median nerve with recording from the m. flexor carpi radialis, radial and musculocutaneous nerves, were not available. Features of demyelination at entrapment sites, which are the elbow segment of the ulnar nerve and the fibular head segment of the peroneal nerve, were not analyzed and did not contribute to the diagnosis of MMN. Responses were only scored if supramaximal stimulation was possible (which is at least 20% above the strength yielding a maximal CMAP; for Erb's point at least 30%). In the case of CB, we ensured that the proximal CMAP did not increase after setting the stimulator at maximal output. If necessary, a collision technique was used to detect effects of co-stimulation.[115,223]
For each nerve the presence of a conduction abnormality was correlated with the presence of weakness (MRC < 5) either in the muscle group innervated by the same nerve (leg nerves) or in the muscle from which the CMAP was recorded (arm nerves). This resulted in the following correlations: median nerve (recording from m. abductor pollicis brevis) with thenar abductors, ulnar nerve with hypothenar abductors, radial nerve with wrist extensors, median nerve (recording from m. flexor carpi radialis) with wrist flexors, musculocutaneous nerve with elbow flexors, deep peroneal nerve with ankle dorsiflexors and tibial nerve with ankle plantarflexors.

Statistical analysis

For the distributions of weakness and electrophysiological abnormalities, statistical significance was calculated using a χ^2 test. A p-value < 0.05 was considered significant. Relations between weakness and electrophysiological abnormalities in one or more segments of the innervating nerve were analyzed by stepwise forward logistic regression, a tool also used to analyse relations between CB and other electrophysiological abnormalities in the same nerve. Relations were expressed by odds ratios (OR) and their 95% confidence interval (95 CI).

Results

Distribution of weakness

The distribution of weakness (MRC < 5) is shown in figure 1 and table 2. Patients showed weakness in 2 up to 15 muscle groups, always including the distal arm muscles. When all muscle groups were included in a χ^2 test, unilateral weakness was found more often than bilateral weakness ($p < 0.01$). Weakness was found significantly more often in distal than in proximal muscle groups and significantly more often in arms than in legs (all $p < 0.01$).

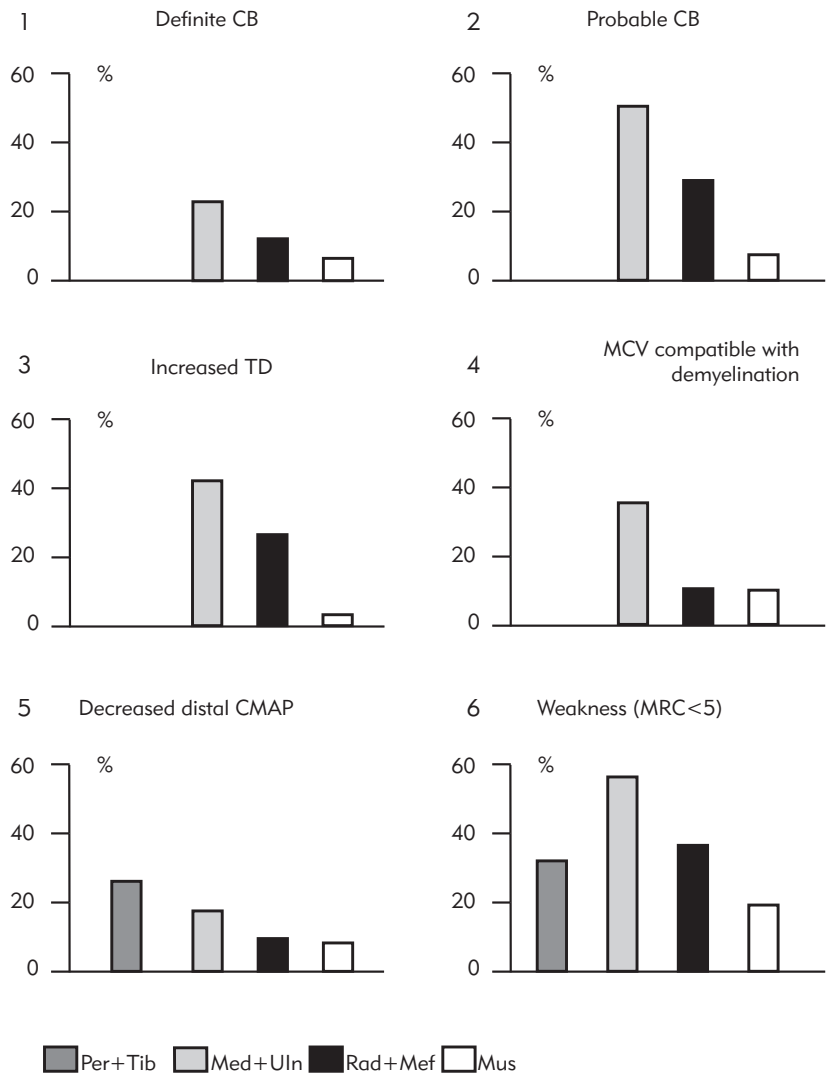


Figure 1. Nerve length and distribution of abnormalities. Each bar represents the cumulated number of abnormalities in the nerve(s) mentioned under the bar, expressed as a percentage of the total number of nerves investigated. CB = conduction block. TD = temporal dispersion. MCV = motor conduction velocity. CMAP = compound muscle action potential. Med = median nerve with recording from the m. abductor pollicis brevis. Uln = ulnar nerve. Mef = median nerve with recording from the m. flexor carpi radialis. Rad = radial nerve. Mus = musculocutaneous nerve. Per = deep peroneal nerve. Tib = tibial nerve.

Table 2. Distribution of muscle weakness in 39 patients

	Number (%) of patients with weakened muscle groups		
	unilateral	*bilateral*	*total*
Arm			
Distal muscle groups	21 (54)	18 (46)	39 (100) [1,3]
Thenar abductors	22 (56)	12 (31)	34 (87)
Hypothenar abductors	21 (54)	14 (36)	35 (90)
Wrist extensors	22 (56)	7 (18)	29 (74)
Wrist flexors	14 (36)	6 (15)	20 (51)
Proximal muscle groups	15 (38)	5 (13)	20 (51) [2,3]
Elbow extensors	10 (36)	0 (0)	10 (26)
Elbow flexors	11 (28)	3 (8)	14 (36)
Arm abductors	10 (26)	3 (8)	13 (33)
Leg			
Distal muscle groups	16 (41)	9 (23)	25 (64) [1,4]
Ankle dorsiflexors	15 (38)	3 (8)	18 (46)
Ankle plantarflexors	15 (38)	8 (21)	23 (59)
Proximal muscle groups	6 (15)	2 (5)	8 (21) [2,4]
Knee extensors	3 (8)	0 (0)	3 (8)
Knee flexors	4 (10)	2 (5)	6 (15)
Hip flexors	4 (10)	0 (0)	4 (10)

Weakened muscle groups (MRC < 5) were scored. Total = uni- or bilateral. [1] = significantly more ($p < 0.01$) more patients with weakness in distal arm than in distal leg muscles. [2] = significantly more ($p < 0.01$) patients with weakness in proximal arm than in proximal leg muscles. [3] = significantly more ($p < 0.01$) patients with weakness in distal arm than in proximal arm muscles. [4] = significantly more ($p < 0.01$) patients with weakness in distal leg than in proximal leg muscles.

Frequency of electrophysiological abnormalities

Examples of recordings are shown in figure 2. The electrophysiologicalal abnormalities in each of the 39 patients are presented in table 3. Definite CB was found in 30 patients, probable CB in 37, increased TD in 33, MCV compatible with demyelination in 25, DML compatible with demyelination in 15, F-M latency compatible with demyelination in 24, F-wave absence in 18 and decreased distal CMAP in 27 patients. Definite CB was found in 65 segments, probable CB in 133, increased TD in 137 and MCV compatible with demyelination in 78 segments. DML compatible with demyelination was found in 24 nerves, F-M latency compatible with demyelination in 42, F wave absence in 26. Electrophysiological abnormalities other than a decreased distal CMAP were found in 220 nerves. A decreased distal CMAP was found in 94 nerves, of which 34 also showed other abnormalities. Electrophysiological abnormalities at entrapment sites were found unilaterally in the elbow segments of the ulnar nerve in 9 patients. They consisted of increased TD and MCV compatible with demyelination. Conduction block was not found at

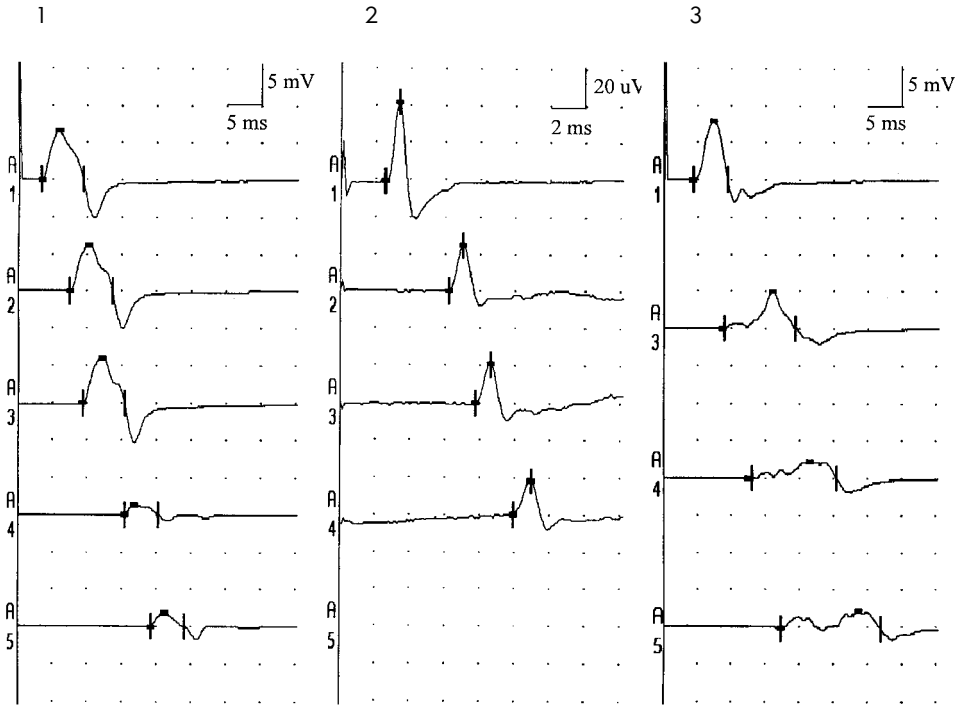
Table 3. Electrophysiological abnormalities in nerves that were associated with weakness (bold) and without weakness (not bold) in the muscle from which the CMAP was recorded

Patient	*Definite CB*		*Probable CB*	
no.	*TD-*	*TD+*	*TD-*	*TD+*
1	**Med^{1}**,**Uln^{13}**,**Rad^{3}**,**Mef^{3}**	**Uln^{1}**	**Med^{1}**,Rad^{3}	Mef^{2}
2	**Med^{3}**,Mef^{3},Mef^{3},Tib	Tib	**Uln^{23}**,**Uln^{2}**,**Rad^{3}**,**Rad^{3}**	
3	Uln^{1},**Uln^{3}**,**Mef^{3}**,**Tib**	-	Med^{3},Mef^{3}	**Mef^{2}**,**Rad^{2}**
4	**Uln^{1}**,**Rad^{2}**,**Mus**	**Med^{1}**,**Mef^{2}**	**Rad^{3}**,**Mef^{3}**,**Mef^{3}**	**Med^{2}**,**Rad^{3}**
5	Med^{3},Mef^{3},**Uln^{1}**	**Mef^{3}**,**Tib**	-	Med^{1},Uln^{2},**Rad^{3}**
6	**Med^{3}**,**Mef^{3}**,Mus^{3}	**Uln^{3}**	**Med^{2}**,Med^{2},**Rad^{3}**	-
7	**Med^{2}**,**Uln^{2}**	**Uln^{1}**	Med^{2},**Mef^{2}**	**Med^{1}**,Med^{1},**Mef^{3}**,Mef^{2},Rad^{2}
8	**Med^{1}**,**Mef^{2}**	-	**Mef^{2}**	**Uln^{3}**
9	**Med^{2}**,**Mef^{2}**	-	-	-
10	Uln^{2}	**Rad^{3}**, Mef^{3}	Rad^{3}	Med^{13},**Med^{12}**,Uln^{3}, **Uln^{123}**,Mef^{2},Mus,**Mus**
11	**Rad^{2}**	**Med^{1}**	Uln^{3}, Rad^{2},**Rad^{3}**	**Med^{1}**,Mef^{3}
12	**Uln^{3}**	Uln^{1}	Rad^{3},**Rad^{2}**,Mus,**Mus**	-
13	**Tib**	**Med^{2}**	**Uln^{1}**	**Med^{1}**,Mef^{2},**Uln^{3}**
14	**Uln^{3}**	-	**Mef^{3}**	**Uln^{1}**
15	Tib	**Med^{3}**	Uln^{2},**Rad^{3}**	**Med^{1}**,**Mef^{2}**
16	Rad^{2}	-	**Med^{3}**,**Mef^{3}**,**Uln^{13}**,**Rad^{3}**	**Med^{2}**, **Med^{23}**,Mef^{3},**Uln^{2}**, Uln^{1},**Mus**
17	**Uln^{1}**	-	**Med^{2}**,**Med^{3}**	**Med^{1}**,**Med^{1}**
18	Tib	-	Med^{2},Med^{1}	**Rad^{3}**
19	Mef^{3}	-	**Med^{3}**,**Uln^{13}**	-
20	**Med^{12}**	-	Mef^{2},**Uln^{1}**	-
21	**Mus**	-	**Mef^{3}**	-
22	**Mef^{3}**	-	**Rad^{3}**	-
23	Med^{2}	-	-	**Med^{1}**
24	**Uln^{3}**	-	-	-
25	**Mus**	-	-	-
26	-	**Uln**, **Tib**	-	Uln^{1}
27	-	**Uln^{1}**	Mef^{2},Rad^{2},Mus	Med^{1},**Uln^{3}**,**Uln^{1}**,**Rad^{23}**
28	-	**Med^{1}**	Mef^{2}	**Med^{1}**,**Uln^{1}**
29	-	Uln^{2}	Med^{1},Uln^{2}	Med^{1}
30	-	**Uln^{2}**	**Uln^{3}**	-
31	-	-	**Mef^{3}**,**Uln^{12}**,**Uln^{1}**	-
32	-	-	**Rad^{3}**,Mef^{3}	Med^{1},**Uln^{3}**
33	-	-	Uln^{3}	**Med^{2}**,**Med^{3}**,Mef^{2},**Uln^{1}**,**Uln^{1}**
34	-	-	**Uln^{3}**	Med^{2},Mef^{2},**Uln^{2}**,Uln^{1}
35	-	-	**Mef^{2}**	**Uln^{3}**
36	-	-	**Uln^{3}**	-
37	-	-	-	Med^{1},**Uln^{2}**
38	-	-	-	**Med^{1}**
39	-	-	-	Med^{1}

CB = conduction block. TD- = without increased temporal dispersion, TD+ = with increased temporal dispersion. MCV = motor conduction velocity compatible with demyelination. DML = distal motor latency compatible with demyelination. F-M = F-M latency compatible with demyelination. Med = median nerve with recording from the m. abductor pollicis brevis. Uln = ulnar nerve. Mef = median nerve with recording from the m. flexor carpi radialis. Rad = radial nerve. Mus = musculocutaneous nerve. Per = deep peroneal nerve. Tib = tibial nerve. Bold = weakness (MRC < 5) of the muscle from which the CMAP was recorded. The numbers refer to the affected segment (0 = distal to the wrist or ankle, 1=lower arm, 2=upper arm, 3=shoulder). The nerves on each side of the body are mentioned separately.

Table 3. continued

Patient	*Features of demyelination other than CB and increased TD*			*Decreased distal CMAP*
no.	*MCV (1-3) / DML(0)*	*F-M*	*F-wave absence*	
1	**Med^{1}**,**Uln^{123}**,Mef^{0},Per^{1}	Per,**Tib**	**Med**,**Uln**,**Uln**,**Per**	**Per**
2	**Med^{3}**,**Med^{3}**,Mef^{03},**Uln^{3}**,**Uln^{012}**, **Rad^{3}**,**Rad^{3}**,Mus^{3}	**Uln**	**Uln**	**Uln**,**Rad**,**Rad**,Mus
3	**Mef^{3}**,**Uln^{2}**,Uln^{1}	Uln,**Uln**,Tib	-	**Med**,**Mef**,**Rad**,**Mus**
4	**Med^{012}**,Mef^{0}	**Med**,**Uln**	**Med**	**Med**,**Uln**,**Uln**,**Per**
5	**Med^{01}**,Med^{3},**Mef^{03}**,**Uln^{1}**,**Rad^{3}**,Mef^{0}	**Uln**,Tib	Med,**Uln**,Per	**Med**,**Uln**,Rad,**Tib**
6	**Med^{3}**,Mef^{03},**Uln^{3}**,**Mef^{0}**,Mus^{3}	-	-	-
7	**Med^{2}**,**Uln^{2}**,**Uln^{1}**	**Uln**,**Uln**	-	**Per**,**Tib**
8	**Med^{01}**,**Med^{1}**,Rad^{2}	-	**Med**,**Med**	**Med**,**Med**,**Uln**
9	-	-	Per	-
10	**Uln^{3}**,**Rad^{3}**,**Mus^{3}**	Med,**Med**, Uln,Tib	-	**Per**
11	**Med^{2}**,**Uln^{01}**,**Rad^{3}**,**Mus^{3}**	**Med**,**Uln**	**Med**	**Uln**,**Per**,**Tib**,Tib
12	-	**Uln**,Per	**Tib**	-
13	**Med^{1}**,Mef^{0}	**Uln**	**Med**	**Med**,**Med**,**Tib**
14	**Med^{0}**,**Mef^{0}**	**Med**	-	**Med,Med,**Uln**,Rad,**Per
15	**Med^{3}**,**Mef^{3}**,**Rad^{3}**	**Med**	-	-
16	**Med^{2,3}**,**Uln^{3}**,**Mef^{2}**	-	-	**Tib**
17	Mef^{0},**Uln^{23}**,**Mus^{3}**,**Per^{0}**	**Med**,**Uln**	-	**Rad**,**Rad**,**Per**,Tib
18	Uln^{2}	**Med**	**Uln**, **Per**	Med,Uln,Per,Per
19	**Uln^{3}**	**Med**,**Uln**, **Per**,Per	-	Per
20	**Med^{2}**,**Uln^{2}**	-	-	-
21	-	-	-	-
22	-	-	-	**Med**,**Uln**
23	-	-	-	-
24	-	-	-	-
25	**Uln^{0}**	Uln	-	**Med**,**Mef**,Uln,**Rad**,**Rad**
26	**Uln^{1}**,Mef^{0}	**Uln**,**Uln**	Per	**Tib**
27	**Mef^{0}**,**Uln^{0}**	**Uln**	**Per**	**Med**,**Mef**,Mus,Per,Tib
28	**Med^{1}**,**Med^{01}**,Mef^{0},Mef^{0},**Mus^{3}**	**Med**,**Uln**	**Med**	**Med**,**Med**,Mef,**Uln**,**Rad**,
29	Uln^{2},Uln^{23}	Uln	-	Per,**Per**,**Tib**,**Tib** **Mus**, Mus,**Per,Per,Tib,Tib**
30	**Med^{3}**,**Uln^{2}**	-	**Uln**	-
31	**Uln^{2,3}**,Mef^{3}	Per	Tib	**Med**,**Rad**,Tib
32	-	-	-	-
33	**Med^{2}**,**Uln^{2}**,**Uln^{1}**	**Med**,**Uln**	**Per**	**Per**,**Tib**,Tib **Mus**,**Per**,**Per**,**Tib**,**Tib**
34	**Uln^{2}**	-	-	Tib
35	**Mef^{0}**	-	-	**Med**
36	**Uln^{3}**,Mef^{2},Mus^{3}	**Uln**	**Per**,**Tib**	**Rad**,**Per**,**Per**,**Tib**,**Tib**
37	**Uln^{2}**,**Mef^{3}**	Med	**Per**	**Med**,**Per**
38	-	-	-	-
39	**Uln^{2}**	-	-	-



	DUR	AMP	AREA	DML MCV
A1 wrist	6.2	6.7	23.3	3.2
A2 elbow d	6.3	6.2	21.9	55
A3 elbow p	6.0	6.4	21.6	55
A4 axilla	4.8	1.4	4.4	23
A5 Erb	4.8	1.9	4.9	58

	DUR	AMP	SCV
A1 wrist	0.8	43.3	56
A2 elbow d	0.8	25.1	61
A3 elbow p	0.9	21.6	77
A4 axilla	1.0	18.1	64

	DUR	AMP	AREA	DML MCV
A1 wrist	5.1	8.0	21.5	4.3
A3 elbow p	10.4	5.0	17.7	54
A4 axilla	12.4	2.6	17.9	49
A5 Erb	14.5	2.5	17.7	51

Figure 2. Conduction studies in patients with MMN. (1) Motor conduction in the right ulnar nerve of patient 7, with recording from the m. abductor digiti V. Definite CB and MCV compatible with demyelination were found in the upper arm segment. (2) Sensory conduction in the same nerve, with recording from digit V. No abnormalities were found. (3) Motor conduction in the right median nerve of patient 17, with recording from the m. abductor pollicis brevis. Increased TD and probable CB were found in the lower arm segment and probable CB was found in the upper arm segment. elbow d = stimulation 5 cm distally from elbow; elbow p = stimulation 5 cm proximally from elbow; DUR = duration in ms; AMP = amplitude in mV or µV; DML = distal motor latency in ms; MCV = motor conduction velocity in m/s; SCV = sensory conduction velocity in m/s. Area in mVms.

entrapment sites. No evidence of demyelination was found in the fibular head segments of the deep peroneal nerve.

Table 4. Comparison of lower arm and lower leg nerve segments

Abnormality		*Number (%) of nerves with abnormality*	
		Median + Ulnar	*Peroneal + Tibial*
Definite CB		14 (10)	7 (6)
Increased TD		37 (28)	24 (19)
MCV compatible with demyelination	*	16 (11)	0 (0)
DML compatible with demyelination	*	9 (6)	1 (1)
F-M compatible with demyelination	*	33 (27)	9 (8)
F-wave absence		14 (10)	12 (10)
Decreased distal CMAP		29 (19)	42 (28)

*CB = conduction block. TD = increased temporal dispersion. MCV = motor conduction velocity compatible with demyelination. DML = distal motor latency compatible with demyelination. F-M = F-M latency compatible with demyelination. CMAP = compound muscle action potential. Definite CB, increased TD and MCV compatible with demyelination were scored in the lower arm and lower leg segments. * = abnormalities were found more often in arm than in leg nerves ($p < 0.05$). Probable CB could not be scored for leg nerves.*

Electrophysiological abnormalities in arm versus leg nerves

To determine whether electrophysiological abnormalities were preferentially located in arm nerves, we compared the number of abnormalities in lower arm segments (median nerve with recording from m. abductor pollicis brevis and ulnar nerve) with the number of abnormalities in lower leg segments (deep peroneal and tibial nerve) (table 4). Upper limb segments were not included as these cannot be investigated in the legs. MCV, DML and F-M latency compatible with demyelination, were found significantly more often in lower arm than in lower leg segments ($p < 0.05$). Definite CB and increased TD were also found more often in lower arm than in lower leg segments, but the difference was not significant. A decreased distal CMAP was found more often in leg than in arm nerves, but the difference was not significant.

Electrophysiological abnormalities in long versus short nerves

To determine whether the number of electrophysiological features of demyelination depends on nerve length, we compared the number of nerves with at least one segment with definite CB, probable CB, increased TD or MCV compatible with demyelination in long (median nerve with recording from m. abductor pollicis brevis and ulnar nerve), intermediate (median nerve with recording from m. flexor carpi radialis and radial nerve) and short (musculocutaneus nerve) arm nerves (Fig. 1.1-1.4). Leg nerves were not included as features of demyelination can only be

assessed in the lower leg. The frequency of definite CB, probable CB, increased TD or MCV compatible with demyelination increased significantly with nerve length ($p < 0.05$).
The number of shoulder segments with electrophysiological features of demyelination did not differ significantly among the different arm nerves indicating that shoulder segments of long arm nerves were not more susceptible to demyelination than those of shorter arm nerves.
Comparison of the number of decreased distal CMAPs in leg nerves (peroneal and tibial), which are the longest nerves, and in long, intermediate and short arm nerves showed that the number of nerves with a decreased distal CMAP increased significantly with nerve length ($p < 0.05$) (figure 1.5).

Electrophysiological abnormalities in distal versus proximal nerve segments

We also investigated whether there is a preferential distal localisation of electrophysiological abnormalities by comparing the distribution of features of demyelination in arm nerves with more than one segment (median nerve with recording from m. abductor pollicis brevis and from m. flexor carpi radialis, ulnar and radial nerves) with a random distribution. For each type of electrophysiological abnormality the cumulated number for each segment (lower arm, upper arm or shoulder) was expressed as a fraction of the total number of that segment that was investigated. Subsequently, these fractions were corrected for the average length of that segment and finally expressed as a percentage of the cumulated fractions of all three segments. The distributions of definite CB, probable CB and MCV compatible with demyelination did not differ significantly from random (χ^2 test). This can also be deduced from figure 3 which shows that these distributions appeared to be similar in lower arm, upper arm and shoulder nerve segments. Only the distribution of increased TD was significantly different from random which could be attributed to a disproportionately high number of lower arm segments with increased TD.
These results indicate that the higher frequency of features of demyelination in longer arm nerves can be explained by the fact that, due to the random distribution, longer arm nerves are more often affected than shorter arm nerves.

Relation between weakness and electrophysiological abnormalities

Both muscle strength and conduction studies of the innervating nerve were determined in 546 muscles (14 nerves for each of the 39 patients), of which 226 (41%) were weakened. Each type of electrophysiological abnormality was found more often in nerves innervating weakened muscles than in nerves innervating non-weakened muscles (table 5). However, a substantial number (approximately one-

Table 5. Relation between weakness and electrophysiological abnormalities

Electrophysiological abnormality	*Number [1] and percentage of nerves with abnormality innervating muscles with :*		*Chance [2] of finding abnormality in nerves innervating muscles with :*	
	MRC < 5	*MRC = 5*	*MRC < 5*	*MRC = 5*
Decreased distal CMAP	69 (73)	25 (27)	0.31	0.08
MCV compatible with demyelination	57 (81)	13 (19)	0.25	0.04
Definite or probable CB	105 (65)	56 (35)	0.46	0.18
Increased TD	68 (57)	52 (43)	0.30	0.16
DML compatible with demyelination	15 (63)	9 (37)	0.09	0.04
F-M compatible with demyelination	29 (69)	13 (31)	0.20	0.08
F-wave absence	18 (69)	8 (31)	0.12	0.05

CB = conduction block. TD = increased temporal dispersion. MCV = motor conduction velocity compatible with demyelination. DML = distal motor latency compatible with demyelination. F-M = F-M latency compatible with demyelination. [1] = cumulated number of arm and leg nerves with an abnormality in one or more segments, innervating weakened or non-weakened muscles. [2] = cumulated number of arm and leg nerves with an abnormality in one or more segments, innervating weakened (or non-weakened) muscles, divided by the total number of weakened (or non-weakened) muscles.

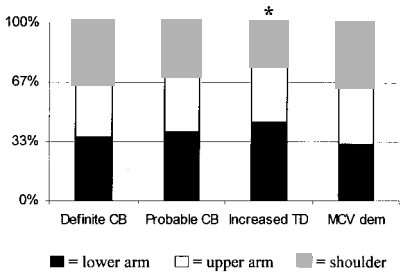


*Figure 3. Distribution of electrophysiological features of demyelination within arm nerves. For each type of electrophysiological abnormality the cumulated number for each segment (lower arm, upper arm or shoulder) was expressed as a fraction of the total number of that segment that was investigated. Subsequently, these fractions were corrected for the average length of that segment and finally expressed as a percentage of the cumulated fractions of all three segments. * significant difference with random distribution ($p < 0.05$). CB = conduction block. TD = temporal dispersion. MCV dem = motor conduction velocity compatible with demyelination.*

third) of electrophysiological abnormalities was found in nerves innervating non-weakened muscles.

Logistic regression analysis of all nerves, of all arm nerves and of long arm nerves (median nerve with recording from the m. abductor pollicis brevis and ulnar nerve) showed significant relations with weakness for a decreased distal CMAP, MCV compatible with demyelination and the presence of CB (table 6). Logistic regression analysis of leg nerves showed a significant relation with weakness for a decreased distal CMAP.

We determined whether CB was related to other electrophysiological abnormalities in the same nerve. Logistic regression analysis showed that CB in nerves innervating weakened muscles was significantly related to MCV compatible with demyelination (OR 9.4, 95 CI 3.9-22.5) and increased TD (OR 10.2, 95 CI 4.5-22.7), but not to a decreased distal CMAP (OR 0.2, 95 CI 0.1-0.5). This indicates that the various features of demyelination are mutually related.

Comparison of electrophysiological protocols

In the present study, all patients underwent an extensive standardized bilateral electrophysiological protocol in a large number of nerves. Using this protocol, all 39 patients were found to have CB or other features of demyelination; in 30 of 39 patients at least one segment with definite CB was found, and in 9 other patients at least one segment with probable CB (table 7). We investigated how these numbers would change if a lower number of nerves had been examined in a bilateral standard protocol, or if the electrophysiological studies had been limited to all or a proportion of those nerves that innervate weakened muscles. Of the 30 patients with definite CB, investigation of the arm nerves revealed definite CB in 29 patients; in only one patient was additional investigation of the leg nerves required to reveal definite CB. Among the arm nerves, most abnormalities were found in the median nerve

Table 6. Relation between muscle weakness and electrophysiological abnormalities in the innervating nerves

	All nerves	*All arm nerves*	*Med + Uln*	*Per + Tib*
Decreased distal CMAP	7.4 (4.3 -12.6)**	9.2 (4.2 - 20.1)**	7.5 (2.2 -25.3)**	6.4 (3.0 - 13.9)**
MCV compatible with demyelination	4.5 (2.3 - 9.0)**	4.4 (2.2 - 8.8)**	5.2 (1.8 -15.0)*	-
Conduction block (definite or probable)	4.0 (2.6 - 6.2)**	4.1 (2.5 - 6.7)**	2.9 (1.3 - 6.4)*	-
Increased TD	-	-	-	-
DML compatible with demyelination	-	-	-	-
F-M compatible with demyelination	-	-	-	-
F-wave absence	-	-	-	-

*Odds ratios and confidence intervals. * $p < 0.01$. ** $p < 0.001$. - = not significant. CMAP = compound muscle action potential. MCV = motor conduction velocity. TD = temporal dispersion. Med = median nerve with recording from the m. abductor pollicis brevis. Uln = ulnar nerve. Per = deep peroneal nerve. Tib = tibial nerve.*

Table 7. Diagnostic yield of different electrophysiological protocols

Investigation	*Number of patients with:*		
	Definite CB	*Definite or probable CB*	*CB or other features of demyelination*
Bilateral standard			
Med + Uln + Rad + Mef + Mus + Per + Tib	30	39	39
Med + Uln + Rad + Mef + Mus	29	39	39
Med + Uln	24	37	37
Rad + Mef + Mus	15	29	33
Per + Tib	7	7	24
Limited to nerves innervating weakened muscles			
Med + Uln + Rad + Mef + Mus + Per + Tib	26	37	38
Med + Uln + Rad + Mef + Mus	26	37	38
Med + Uln	22	34	35
Rad + Mef + Mus	12	23	27
Per + Tib	4	4	14

CB = conduction block. Features of demyelination include increased temporal dispersion, motor conduction velocity, distal motor latency and F-M interval compatible with demyelination, and F-wave absence. Med = median nerve with recording from the m. abductor pollicis brevis. Uln = ulnar nerve. Rad = radial nerve. Mef = median nerve with recording from the m. flexor carpi radialis. Mus = musculocutaneus nerve. Per = deep peroneal nerve. Tib = tibial nerve.

with recording from the m. abductor pollicis brevis and in the ulnar nerve. Protocols consisting of a bilateral standard investigation revealed approximately 10 percent more patients with definite CB, and approximately 5 percent more with definite or probable CB, compared with protocols limited to nerves innervating weakened muscles.

Discussion

In the present study of 39 clinically and electrophysiologically well-defined patients with MMN, all of whom responded to IVIg therapy, we compared the pattern of weakness and electrophysiological abnormalities to identify a possible preferential localisation of features of demyelination or axonal loss and their relation to weak muscle groups. This may have implications for developing electrodiagnostic protocols for MMN and other immune-mediated polyneuropathies. The weakness in our population was more pronounced in the arms than in the legs and more in distal than in proximal muscles which is similar to other reports on MMN.[111,213] Electrophysiological evidence of demyelination was found most often in long arm nerves. For the arm nerves, this phenomenon can be explained by the random distribution of demyelination between lower arm, upper arm and shoulder segments. It is not known if this random distribution also holds true for the most proximal arm nerve segments since we did not perform cervical root stimulation.[103,145] Electrophysiological evidence of axonal loss presented more often in longer nerves and was found most frequently in the legs. Weakness was significantly associated with decreased distal CMAPs, MCV compatible with demyelination and CB. All types of electrophysiological abnormalities were found more often in nerves innervating weakened muscles than in nerves innervating non-weakened muscles, but a substantial number (approximately one-third) of electrophysiological abnormalities was found in nerves innervating non-weakened muscles. For electrodiagnostic examination of patients with lower motor neuron syndromes, these results imply that conduction block or other electrophysiological features of demyelination are most likely to be found in long arm nerves (median and ulnar nerves) innervating weakened muscles, but if conduction block cannot be detected in these, the electrophysiological examination should be extended to other nerves of the arms and legs including those innervating non-weakened muscles.

A decreased distal CMAP can be the result of CB distal to the most distal stimulation site or axonal loss.[2,23] In the present study 156 lower arm and 156 lower leg segments were investigated. CB was found in 50 lower arm segments and a decreased distal CMAP in 29. CB was found in 7 lower leg segments and a

decreased distal CMAP in 42. As CB was shown to be randomly distributed over arm nerve segments and as the lower arm and lower leg segments are about four times longer than the segments distal to the most distal stimulation sites, a decreased distal CMAP is more likely to be caused by axonal loss than by distal CB. In a follow-up study of MMN patients we showed that a decrease in distal CMAP over time occurred more often than development of CB in lower arm or lower leg segments indicating that the decrease in distal CMAP was more likely due to axonal degeneration.[230] Finally, in 5 patients with MMN with a decreased distal CMAP amplitude of the median nerve, we stimulated the recurrent branch to the abductor pollicis brevis muscle distal to the wrist but found no evidence of CB (H. Franssen, unpublished observation). For these reasons we have considered a decreased distal CMAP most likely to be the result of axonal loss.

In MMN, most evidence points to an association of CB with demyelination on the basis of pathophysiological studies[7,35,61,106,167,208], increased signal intensity on MR imaging[237] (this study), and the correlation between CB and MCV compatible with demyelination[61,106] (this study). Alternatively, it has been suggested that CB is the result of blocking of nodal sodium channels[192]; however, up until now no evidence has been obtained for this mechanism.[106] For these reasons, we have considered CB to be the result of demyelination.

All types of electrophysiological abnormality were found most often in nerves innervating weakened muscles, but also in nerves innervating muscles in which weakness was not found according to MRC grading. Relations with weakness were found for axonal loss, MCV compatible with demyelination and CB. Because CB and MCV compatible with demyelination were related to each other, and as it is unlikely that weakness is caused by decreased MCV, weakness is most probably caused by CB or axonal loss. This had been suggested previously but not statistically proven[61] and it is in concordance with the finding that weakness occurred more often in nerves with CB than in nerves with increased TD.[111] The predominant distal localization of weakness can be explained by the random distribution of demyelination in arm nerve segments, leading to more sites with CB in longer arm nerves, and the nerve length dependence of axonal loss in arm and leg nerves. Whether this axonal loss is secondary to demyelination or whether it occurs independently of demyelination is at present unclear. Excitability measurements distal to the site of CB in patients with MMN have revealed evidence of axonal hyperpolarization, thought to be secondary to intra-axonal accumulation of Na^+ ions at the site of CB due to reduced Na^+/K^+ pump activity.[114] The Na^+ accumulation could in turn lead to intra-axonal Ca^+ accumulation due to reversal of the Na^+/Ca^+ pump and, consequently, to axonal degeneration. Such a depolarizing block deteriorates with cooling due to further impairment of the Na^+/K^+ pump[105] in contrast to

a demyelinative block which improves with cooling due to the longer opening time of nodal voltage gated Na^+ channels.[180] However, in a previous study we have found that cooling improves CB as is consistent with a demyelinative rather than a depolarising block.[67] Nevertheless it is possible that, by a mechanism that is unknown at present, the length dependence of axonal loss is due to the random distribution of demyelinating lesions that lead to axonal degeneration. Relations between immune-mediated demyelination and axonal loss were also suggested for chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome, but the exact mechanisms are still not known.[40,74,205]

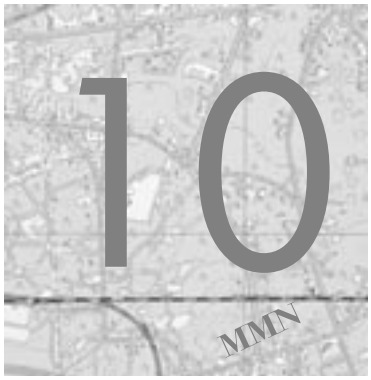
Electrophysiological investigation can be of crucial importance in differentiating MMN from lower motor neuron disease. It remains controversial whether the detection of CB or other features of demyelination is necessary for the diagnosis of MMN. Previous studies concluded that diagnostic criteria for MMN requiring CB may lead to underdiagnosis of this potentially treatable neuropathy.[22,111] On the other hand, we have previously shown that the presence of CB is highly predictive of a beneficial response to IVIg in patients with lower motor neuron syndromes.[231] Comparison of different studies is difficult as the presence of CB in MMN may depend strongly on criteria used for CB and the number of nerves investigated. In the present study we showed that extensive bilateral electrophysiological examination, including arm and leg nerves innervating non-weakened muscles, may improve the diagnostic yield of CB and other features of demyelination. Recently, Katz et al. described 3 patients with a lower motor neuron syndrome without CB or other features of demyelination who responded to IVIg treatment.[109] They suggested that these patients suffered from an immune mediated motor neuropathy with axonal features that was distinct from MMN or other motor neuron syndromes. However, based on the results of our study, MMN cannot be excluded in these patients as the electrophysiological protocol was restricted: in some patients only two limbs were investigated. Alternatively, the patients of Katz et al. might suffer from progressive spinal muscular atrophy as follow up was only 5 months whereas our patients showed a positive response for at least 12 months. We have previously described 5 patients with a lower motor neuron syndrome without CB or other features of demyelination, according to our protocol, who did not respond to IVIg with the exception of one patient who responded for 6 months but deteriorated thereafter.[223] This issue can only be solved if the response to IVIg is investigated in a large group of patients with a lower motor neuron syndrome without evidence of CB or other features of demyelination according to an extensive electrodiagnostic protocol. The detection of CB in such future studies might be further improved by fatiguability testing[103] or root stimulation[103,145] both of which were shown to reveal CB in nerves in which CB was not found on conventional nerve conduction

studies.

The question arises why demyelination is found predominantly in arm nerves and axonal loss predominantly in leg nerves. A possible factor is that demyelination in leg nerves cannot be detected because of the relative inaccessibility of proximal leg nerve segments to electrophysiological investigation. Although it has been shown that lumbar root stimulation can detect proximal demyelination in MMN[145] , this cannot explain the total absence in our study of MCV compatible with demyelination in lower leg segments including those with normal distal CMAPs. The absence of F waves, as was found in a number of leg nerves in this study, cannot be interpreted as proximal demyelination because it was also found in patients with motor neuron disease.[174] Together with the predominance of weakness in arm nerves, these findings point to different pathophysiological mechanisms for arm and leg nerves which might be related to differences in ion channel distributions. This is supported by the finding that in normal subjects accommodation to subthreshold depolarizing currents was greater for median than for deep peroneal nerve motor fibres, suggesting that median nerve motor fibres express more outward rectifying slow K^+ channels than deep peroneal nerve motor axons; inward rectification was not different between these nerves.[119] As demyelination exposes paranodal or internodal K^+ channels, demyelination in an arm nerve as compared to that in a leg nerve, might lead to a greater outward K^+ current, more hyperpolarization and, consequently, a greater susceptibility to CB.[103]

In conclusion, this study shows that, in MMN, the distribution of demyelination is random in arm nerves, and that the distribution of axonal loss is nerve length-dependent. 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. In combination with the correlation of features of demyelination and axonal loss with weakness, these distributions can explain the typical pattern of weakness in MMN. These results have implications for the way in which the electrophysiological examination is conducted in a patient suspected of MMN. In addition they may help one to understand the pathophysiological mechanisms that are involved in MMN and in fibre length dependency of abnormalities in immune-mediated neuropathies.

Disease severity in multifocal motor neuropathy and its association with the response to immunoglobulin treatment



RM Van den Berg-Vos, H Franssen, J Visser, M de Visser, RJ de Haan,
JHJ Wokke, LH Van den Berg

Journal of Neurology 2002; 249: 330-336.

Introduction

Multifocal motor neuropathy (MMN) is a chronic disorder of the peripheral nervous system characterized by asymmetrical weakness of limbs without sensory loss. The presence of motor conduction block outside entrapment sites, which also occurs in chronic inflammatory demyelinating polyneuropathy (CIDP), and elevated serum antibodies to GM1 ganglioside support an immune-mediated pathogenesis and have led to various studies of immunological treatment of MMN.[8,12,14,28,34,50,62,131,132,153,155,170,176,185,224,243] Corticosteroids and plasma exchange appeared to be ineffective in most patients with MMN, but treatment with cyclophosphamide, which may have serious side-effects, or high-dose intravenous immunoglobulins (IVIg) have shown a beneficial effect on muscle strength in several open and placebo-controlled studies. The effect of IVIg treatment, however, only lasts for a number of weeks in most patients and long-term IVIg maintenance treatment, which is expensive and burdensome for the patient, is often required to sustain muscle strength.

In contrast to CIDP, a relapsing/remitting course of MMN has not been reported. The natural course of MMN is supposed to be slowly progressive, but a prospective study is not feasible as most patients receive immunological treatment. It is not known to what extent muscle weakness might progress over time if not treated, nor whether progression is due to an ongoing immune-mediated process in motor nerves. Investigating these matters is important if long-term treatment strategies with immunosuppressive agents or IVIg are to be justified.

In the present study of 38 MMN patients, we retrospectively describe the course of the disease by assessing disease severity in patients with a disease duration ranging from 6 months to 34 years. As indicator for an ongoing immune-mediated disease, we measured the response to one course of IVIg treatment and subsequently associated response to treatment with disease severity.

Patients and methods

Patients

We included 38 patients on the basis of three criteria: (1) the presence of asymmetrical limb weakness at onset, or a distribution of muscle weakness at examination with at least two peripheral nerves affected and at least one muscle group demonstrating disabling weakness of MRC grade 4 or less; (2) electrophysiological evidence of motor conduction block in at least one nerve according to previously published criteria[231]; (3) the patient had not received any immunological treatment previously.

Patients were diagnosed at the neuromuscular outpatient clinics of the University Medical Center Utrecht and the University of Amsterdam, both national referral centers for the diagnosis and treatment of motor neuron disease and MMN. Patients who had bulbar signs or symptoms, or upper motor neuron signs (spasticity or hyperreflexia or extensor plantar response) were excluded. Mild sensory symptoms were permitted as long as there were no sensory deficits on examination, and sensory nerve conduction studies were normal. All patients were tested for serum IgM anti-GM1 antibodies as described elsewhere.[228] Magnetic resonance (MR) imaging of the brachial plexus was performed according to a protocol described previously.[237]

Thirty-four patients were treated with one full course of IVIg (0.4 g/kg for 5 days) (Gammagard, Hyland Baxter). Three patients, who had disease durations of 1, 2 and 10 years, were not treated with IVIg as the weakness only affected the intrinsic hand muscles and did not interfere with activities of daily life. One patient with a disease duration of 26 years rejected treatment.

Assessment of disease severity

Two neurologists (RvdB-V and LvdB) examined the patients included in the study. Disease duration was measured from the onset of limb weakness. Disease severity was assessed for each patient at inclusion by: (a) the number of affected limb regions; (b) muscle strength; (c) functional impairment; and (d) electrophysiological studies, and these variables of disease severity were correlated with disease duration. The *number of affected limb regions* was assessed by dividing each limb into two regions, that is upper arm, lower arm, upper leg, lower leg on both sides (maximally eight affected regions). *Muscle strength* was measured according to the Medical Research Council (MRC) scale[142] in five muscle groups in both arms (shoulder abduction, elbow flexion, elbow extension, wrist flexion and wrist extension) and five muscle groups in both legs (hip flexion, knee flexion, knee extension, ankle dorsiflexion, ankle plantarflexion), giving a maximal MRC-sumscore of 100. *Functional impairment* was assessed using the Guy's Neurologic Disability Scale[199] : functional impairment of the upper limbs was scored as follows: 0 = no upper limb problem, 1 = problems in one or both arms, not affecting functions such as fastening zips or buttons, tying a bow in laces or strings, washing or brushing hair and feeding, 2 = problems in one or both arms affecting some but not preventing any of the functions listed, 3 = problems in one or both arms, affecting all or preventing one or two of the functions listed, 4 = problems in one or both arms preventing three of the functions listed, 5 = unable to use either arm for any purposeful movements; functional impairment of the lower limbs was scored as follows: 0 = walking is not affected, 1 = walking is affected but patient is able to walk independently, 2 = usual-

ly uses unilateral support (stick, ankle-foot orthoses) to walk outdoors but walks indepently indoors, 3 = usually uses bilateral support to walk outdoors, or unilateral support to walk indoors, 4 = usually uses wheelchair to travel outdoors, or bilateral support to walk indoors, 5 = usually uses a wheelchair indoors. The *electrophysiological studies* were performed by the same examiner (H.F.). Nerve conduction on both sides was measured using surface electrodes. Prior to an investigation, the arms and legs were warmed in water at 37° C for at least 30 minutes.[67] Motor nerve conduction was investigated up to the axilla in the median nerve (recording m. abductor pollicis brevis), ulnar nerve (recording: m. abductor digiti V) and up to the popliteal fossa in the deep peroneal nerve (recording: m. extensor digitorum brevis). In most patients additional nerves or nerve segments were investigated, but to compare the electrophysiological studies in all patients only the results of the median, ulnar and peroneal nerves were used. The amplitude, area and duration of the negative part of each CMAP were determined. Definite conduction block was defined as a reduction in CMAP area on distal versus proximal stimulation of at least 50%[68,181] and probable conduction block as a reduction in CMAP amplitude of at least 30% in an arm nerve.[2,231] Conduction block was only considered when the CMAP amplitude on distal stimulation of the segment exceeded 1 mV. Evidence of conduction block at entrapment sites was excluded. If necessary, a collision technique was used to detect effects of co-stimulation.[115] For each nerve we determined: the distal amplitude (mV), that is the amplitude of the CMAP on stimulation of the most distal site of the nerve, and the proximal amplitude (mV), the amplitude of the CMAP on stimulation of the most proximal site of the nerve. For each patient we determined the mean distal amplitude (mV), the mean proximal amplitude (mV), the percentage of segments with definite conduction block and the percentage of segments with definite or probable conduction block, of all nerves studied.

Association of disease severity and treatment response

For the assessment of the response to one course of IVIg treatment we used muscle strength measurements before and two weeks after treatment. To determine whether specific variables of disease severity are associated with being a responder to IVIg treatment, we defined 'responders' and 'non-responders' according to criteria that we described in previous studies.[225,226,231,233] In brief, a patient is a 'responder' if muscle strength improves by 50% or more in at least two clinically affected muscles or muscle groups, without a decrease of 25% or more in muscle strength in more than one muscle or muscle group using a hand-held dynamometer[235], or a 'non-responder' if the patient does not respond according to these criteria. To determine whether specific variables of disease severity are associated with a better response to IVIg treatment, we dichotomized the group of 'responders' in patients

with a treatment response of < 2 or ≥ 2 on the MRC-sumscore.
The independent variables for disease severity that were chosen to associate with the response to IVIg treatment were arbitrarily defined as: upper or lower limb involvement, number of affected limb regions < or ≥ 4, number of affected peripheral nerves causing muscle weakness 2 or > 2, MRC-sumscore ≤ or > 95, disability-score < or ≥ 4, mean distal CMAP-amplitude < or ≥ 5.0 mV, mean proximal CMAP-amplitude < or ≥ 4.4 mV, percentage of segments with definite CB ≤ or > 10 and the percentage of segments with definite or probable CB ≤ or > 10. Other independent variables that were associated with the response to treatment were: disease duration < or ≥ 5 years, and age at onset of disease < or ≥ 40 years.

Statistics

Of the variables of disease severity that were correlated with the disease duration statistical significance was calculated using the Kruskal-Wallis test. The impact of the variables of disease severity on the response to IVIg treatment was univariately analyzed with a Chi-square or Fisher-Exact test and expressed in relative risks (RR) with their 95% confidence intervals (95% CI). A p-value < 0.05 was considered to be significant.

Results

Patients

The clinical and laboratory features of the 38 patients are shown in table 1. The disease duration was less than 5 years in 16 patients, between 5 and 10 years in 12 patients, between 10 and 20 years in 8 patients and more than 20 years in 2 patients. The upper limbs were first affected in 22 patients and the lower limbs in 16 patients. At the time of inclusion, 13 of the 22 patients with onset in the upper limbs were still only affected in the upper limbs; 14 of the 16 patients with onset in the lower limbs were also affected in the upper limbs, and in 5 of them weakness was more pronounced in the upper than in the lower limbs. Twelve of the patients demonstrated a distribution of muscle weakness with only two peripheral nerves affected at the time of inclusion; in 26 patients more than two peripheral nerves were affected. Reasons for referral were suspected motor neuron disease (n= 14), polyneuropathy (n= 8), mononeuropathy (n=6), suspected MMN (n=5), radiculopathy (n= 4) and myopathy (n=1).

Table 1. Clinical and laboratory features of 38 patients

Clinical features	
Male sex (n(%))	30 (79)
Age at onset (median (yrs); range)	33.5 (20 - 58)
Disease duration (median (yrs); range)	5.0 (0.5 - 34)
No. of affected regions[1] (median (yrs); range)	3.0 (1 - 7)
MRC-sumscore (median; range)	95.0 (82 - 100)
Laboratory features	
Elevated anti-GM1 antibodies[2] (n(%))	9 (27)
Abnormal MR imaging brachial plexus[3] (n(%))	14 (42)
Electrophysiological features	
Mean distal CMAP-amplitude (median (mV); range)	6.6 (1.6 - 12.6)
Mean proximal CMAP-amplitude (median (mV); range)	4.4 (0.8 - 10.7)
No. of definite CBs (nerve)	32 in 22 patients (17 ulnar, 15 median)
No. of probable CBs (nerve)	41 in 23 patients (18 ulnar, 23 median)
% of segments with definite CB (median)	10.0
% of segments with definite or probable CB (median)	22.5

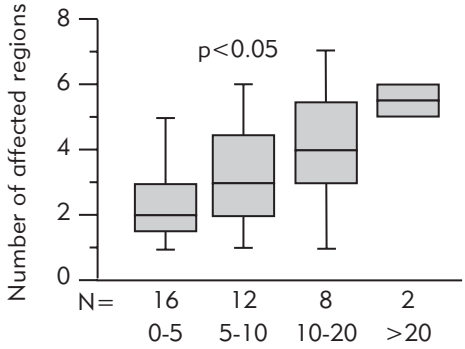
[1] = upper arm, lower arm , upper leg and lower leg on both sides (maximally 8). [2]= investigated in 33 patients. Abnormal MR imaging plexus brachialis = swelling and/or increased signal intensity. [3]= investigated in 33 patients. CMAP= compound muscle action potential. CB= conduction block. No. = number.

Disease severity and its relation to disease duration

Patients with long disease duration had significantly higher numbers of affected regions and significantly lower MRC-sumscores than patients with short disease duration (figures 1.1 and 1.2). The highest disability score in our patients was 4 for upper limbs and 3 for lower limbs. The disability-scores were significantly higher in patients with long disease duration than in patients with short disease duration (figure 1.3). Electrophysiological studies showed that patients with long disease duration had significantly lower mean distal and proximal amplitudes than patients with short disease duration (figure 2.1 and 2.2). The percentage of segments with definite conduction block, and the percentage of segments with definite or probable conduction block were higher in patients with long disease duration than in patients with short disease duration (figure 2.3 and 2.4), although this was only significant when patients with a disease duration $<$ and $\geq$ 10 years were compared (Mann-Whitney U-test, $p < 0.05$).

Association of disease severity and treatment response

Four of the 34 patients who received IVIg treatment were non-responders according to the previously defined criteria. They all received a second full IVIg-course of



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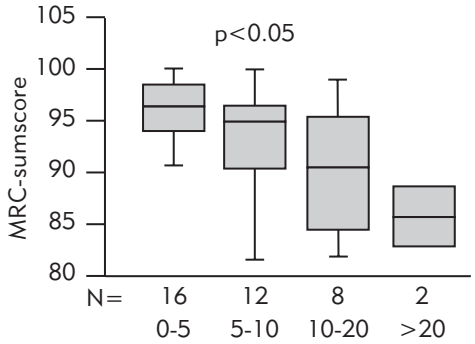

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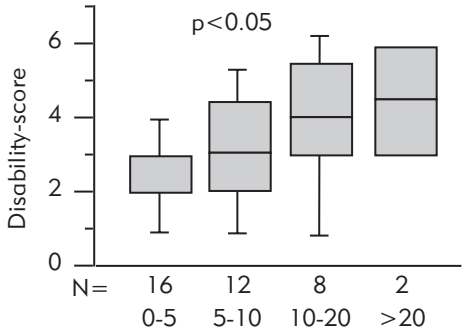

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Figure 1. Boxplots with median value (horizontal bar) , 25th – 75th interquartile range (box), maximum and minimum values of variables per category of disease duration: 1.1 Number of affected regions. 1.2 Muscle strength. 1.3 Disability.

five consecutive days and none of them have responded favourably on this second course. The disease duration of these four patients was 3, 9, 15 and 37 years. Non-responsiveness was not associated with any of the independent variables. Seventeen patients had a treatment response of ≥ 2 on the MRC-sumscore. Univariate analysis showed that two variables (number of affected peripheral nerves causing muscle weakness > 2 and MRC-sumscore ≤ 95) were significantly associated with a treatment response ≥ 2 on the MRC-sumscore (table 2). Figure 31 shows that the median treatment response is larger in the patients with a disease duration of 5 - 10 and

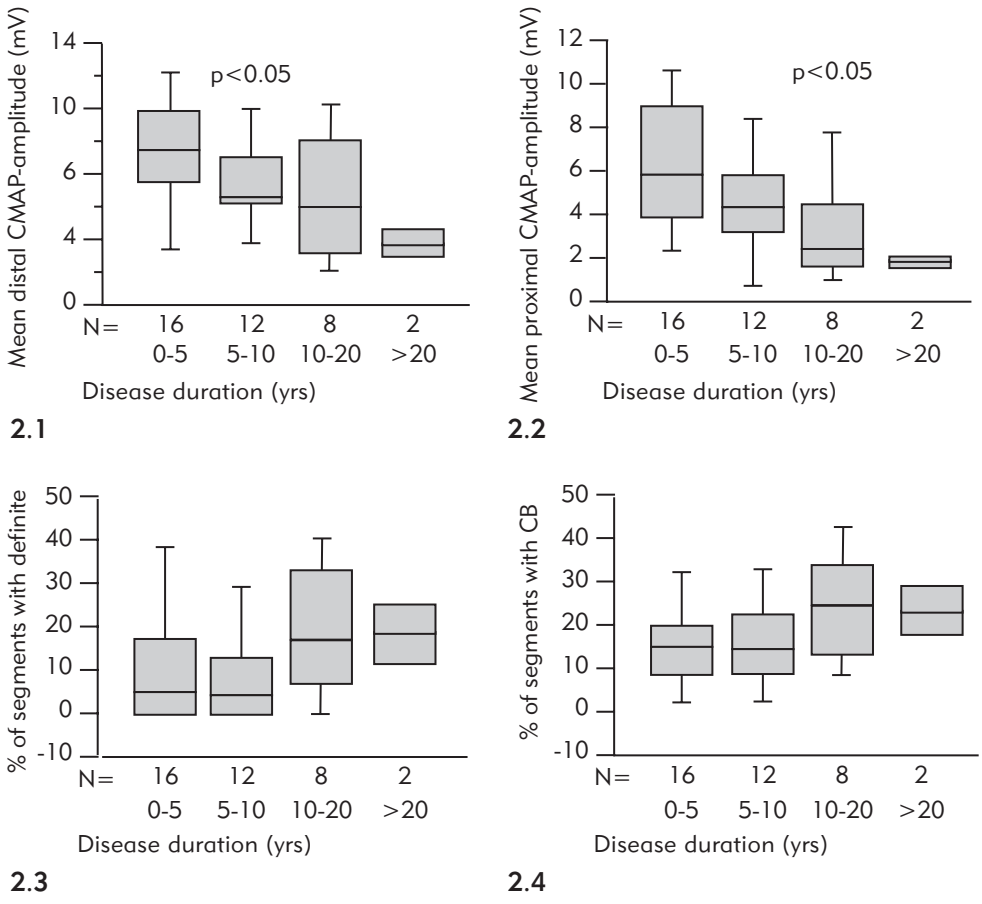

Figure 2. Boxplots with median value (horizontal bar) , 25th – 75th interquartile range (box), maximum and minimum values of electrophysiological variables per category of disease duration: 2.1 Mean distal CMAP-amplitude. 2.2 Mean proximal CMAP-amplitude. 2.3 Percentage of segments with definite conduction block. 2.4 Percentage of segments with definite or probable conduction block.

10 - 20 years than in those affected for 0 - 5 years. However, when the response to treatment was adjusted for the extent of weakness before treatment (= improvement on the MRC-sumscore/(100 - MRC-sumscore before treatment)), the median response to treatment was similar in patients with a disease duration up to 20 years (figure 3.2).

Table 2. Variables of disease severity and associated relative risks of patients with a treatment response ≥ 2 on the MRC-sumscore

Variable	*Prevalence (%)* *N = 34*	*% Treatment - response > 2** *N = 17*	*RR*	*95% CI*	*p-value*
Upper limb involvement	29	29			
Lower limb involvement	71	71	1.00	0.48 - 2.09	1.00
No. of affected regions < 4	68	39			
No. of affected regions ≥ 4	32	73	1.86	0.99 - 3.47	0.14
No. of aff. peripheral nerves 2	26	11			
No. of aff. peripheral nerves > 2	74	89	0.17	0.03 - 1.13	0.02**
MRC-sumscore ≤ 95	62	67			
MRC-sumscore > 95	38	23	0.35	0.12 - 0.98	0.03**
Disease duration < 5 years	41	43			
Disease duration ≥ 5 years	59	55	1.28	0.62 - 2.64	0.73
Upper + lower limb disability-score < 4	62	38			
Upper + lower limb disability-score ≥ 4	38	69	1.82	0.94 - 3.50	0.16
Mean distal CMAP-amplitude < 5.0 mV	26	78			
Mean distal CMAP-amplitude ≥ 5.0 mV	74	40	0.51	0.28 - 0.93	0.12
Mean proximal CMAP-amplitude < 4.4 mV	53	56			
Mean proximal CMAP-amplitude ≥ 4.4 mV	47	44	0.97	0.39 - 1.57	0.73
Percentage definite CB ≤ 10	53	39			
Percentage definite CB > 10	47	63	1.61	0.80 - 3.21	0.30
Percentage definite or probable CB ≤ 10	32	27			
Percentage definite or probable CB > 10	68	61	2.23	0.81 - 6.18	0.14
Age at onset < 40 years	68	39			
Age at onset ≥ 40 years	32	73	1.86	0.99 - 3.47	0.14

** = on the MRC-sumscore. RR = relative risk. 95% CI = 95% confidence interval. ** = significant. CMAP = compound muscle action potential. CB = conduction block.*

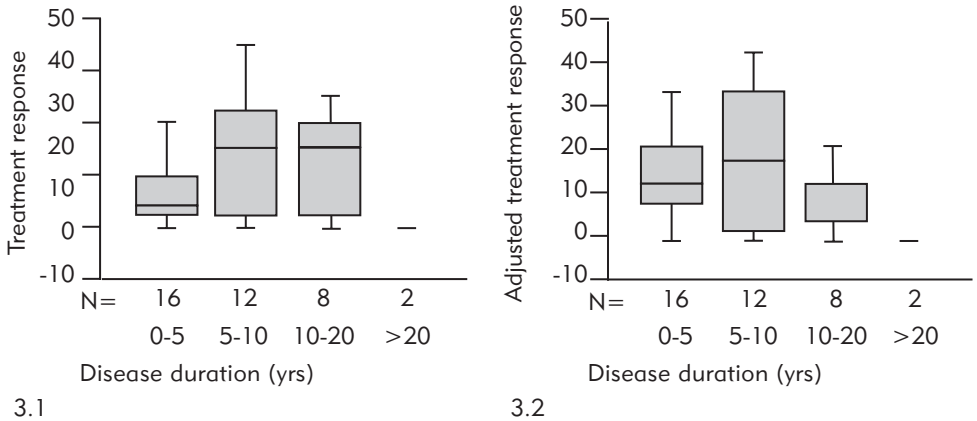

Figure 3. Boxplots with median value (horizontal bar) , 25th – 75th interquartile range (box), maximum and minimum values per category of disease duration of: 3.1 Treatment response. 3.2 Adjusted treatment response (for definition see text).

Discussion

In our study of 38 patients with MMN who had never received immunological treatment and had a disease duration ranging from 6 months to 34 years, patients with a long disease duration had significantly more severe weakness, disability and electrophysiological abnormalities than patients with a short disease duration. In addition, none of our patients experienced spontaneous improvement or a relapsing/remitting disease course. Although we did not perform a prospective study, these results provide evidence for a slowly progressive disease course in MMN. Selection bias may have influenced our study population as relatively mildly affected patients may not have been referred to our neuromuscular outpatient clinic. Nevertheless, nine of our patients had a disease duration of less than one year and four had only weakness of hand muscles at the time of referral. A previous study also estimated a slowly progressive course of MMN, but used a different approach.[213] Eighteen patients were studied with a median follow-up of 37 months and demonstrated a slowly progressive decline on a weakness subscore of the neuropathy impairment score (NIS). This study, however, included both treated and untreated patients.

In our population, patients with a disease duration of up to 20 years showed a good response to IVIg treatment, indicating that progression in MMN may be the result of a chronic ongoing immunological disease. In several smaller studies on IVIg treatment in MMN, patients with a relatively long disease duration were also included who responded favourably to IVIg.[8,9,14,28,34,50,132,155,213] A minority of our patients with MMN did not respond to IVIg treatment. No association was found between non-responsiveness and any of the clinical and electrophysiological features, but the number of non-responding patients was low. Non-responsiveness may be explained by the fact that the immunological disease has been extinguished in a minority of patients. Alternatively, these patients may respond to more aggressive immunosuppressive treatment, although there have been no reports of MMN patients not responding to IVIg and yet responding to immunosuppressive treatment.

When assessing the impact of clinical and electrophysiological variables on the extent of treatment response, more than two affected peripheral nerves causing muscle weakness and a MRC-sumscore of ≤ 95 appeared to be the only variables that, when univariately tested, were significantly associated with a treatment response ≥ 2 on the MRC-sumscore. This can be explained by the higher number of weak muscle groups that may improve by IVIg treatment in patients with a lower pretreatment MRC-sumscore in whom the distribution of muscle weakness is more widespread. Patients with only minor weakness and a MRC-sumscore of 98 or 99 may improve to (almost) normal muscle strength (MRC-sumscore of 99 or 100),

while patients with more severe weakness (MRC-sumscore ≤ 95) may show a greater improvement on the MRC-sumscore but remain relatively weak in several muscle groups. It is important to note, however, that our results emphasize that severely affected patients may still benefit from treatment.

The electrophysiological studies are also consistent with a slowly progressive disease course. The mean distal and proximal amplitudes were lower and the percentage of segments with conduction block was higher in patients with long disease duration. The lower distal amplitude probably reflects more axonal loss but possibly also more distal conduction block, whereas lower proximal amplitude reflects the combined effects of more conduction block, temporal dispersion or axonal loss along the entire length of the nerve.

To assess functional impairment we used two subscales of the Guy's Neurologic Disability Scale, which was originally developed for multiple sclerosis.[199] Although the validity and the inter- and intra-rater reliability of this disability scale have not been tested in patients with MMN, it may be more sensitive to changes in functional impairment of upper and lower limbs experienced by patients with MMN than the modified Rankin scale that was used in previous studies.[225,226,233] Patients with longer disease duration experienced more functional impairment in activities of daily life such as fastening zips or buttons, tying a bow in laces or strings, washing or brushing hair and feeding. The disability in upper limbs was more pronounced than in lower limbs, which is consistent with more pronounced weakness in upper than in lower limbs in MMN. None of our patients had severe disability such as being unable to use either arm for any purposeful movements, needing a wheelchair to travel outdoors or bilateral support to walk indoors.

The results of our study indicate that MMN is a slowly progressive immune-mediated neuropathy. These findings may imply that early treatment may prevent future progression of weakness and disability in patients with MMN.

Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment

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Introduction

Multifocal motor neuropathy (MMN) is characterized by a slowly progressive, asymmetrical weakness of the limbs without sensory loss. Substantial evidence for an immune-mediated pathogenesis of MMN[26,117,131,153,171,243] has led to studies of immunological treatments. Prednisolone and plasma exchange are ineffective in most patients, and of the immunosuppressants only cyclophosphamide seems to be effective but has major side-effects.[10,143,146,173] Various open and placebo-controlled studies have shown that treatment with high-dose intravenous immunoglobulins (IVIg) leads to improvement of muscle strength in patients with MMN.[8,14,28,62,132,155,224] However, as the effect of IVIg treatment lasts only several weeks, IVIg maintenance treatment is necessary to maintain the effect on muscle strength in most patients. Maintenance IVIg treatment is expensive, and the frequent infusions may be burdensome to patients, but at present there is no therapeutic alternative to IVIg therapy. Therefore, studies of the long-term effect of IVIg treatment are important. In most studies of the effect of IVIg treatment, patients were followed for several months[8,14,28,34,57,107,132,155,224,226]; in two studies patients received IVIg maintenance treatment for up to four years, but these studies were relatively small.[9,225]

Evidence of motor nerve conduction block is considered the electrodiagnostic hallmark of MMN. The results of previous studies of the effect of IVIg treatment on motor nerve conduction are not consistent. An improvement in conduction block after several months of IVIg treatment has been described in some studies but others could not detect significant differences on electrophysiological examination.[14,28,34,132,155,224,226]

In the present study, we measured the long-term effect of IVIg maintenance treatment on muscle strength and disability in 11 patients with MMN who had been treated with IVIg for 4 to 8 years. In addition, we performed a systematic long-term analysis of the changes in motor nerve conduction during IVIg treatment and attempted to explain these changes in terms of remyelination, reinnervation, demyelination, or axonal loss.

Patients and methods

Patients

Eleven patients were included who met the following four criteria: (1) clinically, the presence of asymmetrical limb weakness at onset or motor involvement having a motor nerve distribution in at least two peripheral nerve distributions, predominant

upper limb involvement, disabling weakness Medical Research Council (MRC)[142] grade 4 or less in at least one muscle[92], (2) electrophysiological evidence of one site with definite motor conduction block or one site with probable conduction block according to previously defined criteria[231], (3) response to IVIg according to criteria that were described in previous studies[225,226,231,233], and (4) IVIg maintenance treatment lasting at least four years. Patients who had bulbar signs or symptoms, or upper motor neuron signs (spasticity, hyperreflexia, extensor plantar response) were excluded. Mild sensory symptoms were not an exclusion criterion provided that there were no sensory deficits on examination, and the results of sensory nerve conduction studies were normal. The clinical and laboratory features of the 11 patients are described in table 1. The follow-up during IVIg maintenance treatment ranged from four to eight years. Data for the maximally four-year follow-up of patients 1-6 have been reported earlier.[225] Serum IgM anti-GM1 antibody detection[228] and magnetic resonance (MR) imaging of the brachial plexus were performed as described previously.[237]

Study design

Patients were treated initially with one full course of IVIg (0.4 g/kg for 5 days) (Gammagard, Hyland Baxter, Calif., USA), followed by one IVIg infusion every week during the first year of IVIg maintenance treatment.[225] The dosage and frequency of IVIg infusions during the remainder of the follow-up were tailored to each patient on the basis of functioning in daily life. If patients reported that functioning in daily life remained stable or improved the maintenance dose was not changed. If patients deteriorated in their functioning in daily life, we used the results of hand held dynamometry (see below) to titrate the increase in maintenance dose of IVIg for that individual patient. In patients 2, 3, and 4, an intravenous access system (PORT-A-CATH, Pharmacia) was implanted, which enabled them to receive IVIg infusions at home supervised by a nurse as part of the home-care programme of our hospital. During follow-up, we measured muscle strength, disability, and electrophysiological changes as described below.

Assessment of muscle strength

The strength of five muscles or muscle groups of each arm (those involved in shoulder abduction, elbow flexion, elbow extension, wrist flexion and wrist extension) and of five muscles or muscle groups of each leg (those involved in hip flexion, knee flexion, knee extension, ankle dorsiflexion, ankle plantar flexion) was measured bilaterally using the MRC scale, yielding a maximal MRC sumscore of 100. In addition, we performed hand-held dynamometry in a selection (i.e. those muscle groups with an MRC score < 5 on more than one occasion) of the following muscle

Table 1. Clinical, laboratory and IVIg treatment features of 11 patients with multifocal motor neuropathy

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Clinical features											
Sex	M	M	F	M	M	M	M	M	M	M	M
Age at onset (years)	47	30	31	42	30	43	20	48	40	38	58
Site of onset	UL	LL	UL	UL	UL	LL	LL	UL	UL	LL	LL
Disease duration at onset of treatment (years)	6	8	2	7	3	6	4	2	6	12	2
MRC sumscore before follow-up	82	77	97	95	98	96	95	96	92	87	94
MRC sumscore after the first full course of IVIg	89	78	98	99	98	99	100	99	98	91	96
MRC sumscore at the last follow-up examination	86	77	99	99	97	96	97	98	97	91	96
Disability UL before follow-up	4	3	2	2	3	2	0	3	3	3	2
Disability UL after the first full course of IVIg	2	3	1	0	2	2	0	2	2	3	1
Disability UL at the last follow-up examination	3	3	2	0	3	2	1	0	1	3	1
Disability LL before follow-up	0	3	0	0	0	1	1	0	2	2	1
Disability LL after the first full course of IVIg	0	3	0	0	0	0	0	0	1	2	1
Disability LL at the last follow-up examination	0	3	2	0	0	1	1	0	1	2	1
Laboratory features											
CSF protein (g/L)	0.65	0.46	0.18	0.39	0.73	-	0.56	-	0.76	-	0.29
Elevated anti-GM1 antibodies	No	No	No	No	No	No	No	No	No	Yes	No
Abnormal MR imaging brachial plexus	Yes	Yes	No	-	Yes	No	Yes	No	Yes	Yes	No
IVIg treatment											
Follow-up maintenance IVIg (years)	8	8	7	6	6	5	6	4	4	4	4
IVIg dosage per week (g/kg body weight) during follow-up	0.2	0.5	0.4	0.4	0.3	0.1	0.1	0.2	0.2	0.3	0.2
No. of weeks between IVIg infusions during follow-up	6	3	1	2	2	2	7	1	2	5	2

M = male, F = female. UL = upper limb, LL = lower limb. IVIg = intravenous immunoglobulins. CSF = cerebrospinal fluid. MR = magnetic resonance. - = not performed.

groups (shoulder abduction, elbow flexion, elbow extension, wrist extension, hand grip, hip flexion, knee flexion, knee extension, and ankle dorsiflexion). Muscle strength was measured before the onset of IVIg treatment, within 2 to 3 weeks after the initial full IVIg course, and once a year during follow-up.

Assessment of disability

Upper and lower limb disability was scored using two disability subscales of the Guy's Neurological Disability Scale[199], before the onset of IVIg treatment, after the first full course of IVIg and at the last follow-up examination. Disability of the upper limbs was scored as: 0 = no upper limb problem; 1 = problems in one or both arms, not affecting functions such as doing zips or buttons, tying a bow in strings, washing or brushing hair and feeding; 2 = problems in one or both arms affecting some but not preventing any of the functions listed; 3 = problems in one or both arms, affecting all or preventing one or two of the functions listed; 4 = problems in one or both arms preventing three of the functions listed; 5 = unable to use either arm for any purposeful movements. Disability of the lower limbs was scored as: 0 = walking is not affected; 1 = walking is affected but patient is able to walk independently; 2 = usually uses unilateral support (stick, arm or ankle foot orthoses) to walk outdoors but walks independently indoors; 3 = usually uses bilateral support to walk outdoors, or unilateral support to walk indoors; 4 = usually uses wheelchair to travel outdoors, or bilateral support to walk indoors; 5 = usually uses a wheelchair indoors.

Electrophysiological studies

All electrophysiological studies were performed by the same examiner (H.F.). Motor nerve conduction was measured with surface electrode electromyography (EMG) on both sides. Prior to an investigation, the arms and legs were warmed in water at 37° C for at least 30 minutes.[67] Motor nerve conduction was analyzed up to the axilla in the median (recording m. abductor pollicis brevis), and ulnar (recording: m. abductor digiti V) nerves and up to the popliteal fossa in the deep peroneal (recording: m. extensor digitorum brevis) nerve. Additional nerves or nerve segments were investigated to establish the diagnosis of MMN; the results were not analysed because these nerves were not investigated in all patients.

For each compound muscle action potential (CMAP) the amplitude and area of the negative part were determined. For each nerve segment the amplitude reduction on proximal versus distal stimulation (P/D) and area reduction P/D, calculated as (distal CMAP - proximal CMAP)100% / distal CMAP were determined. For each nerve the distal amplitude (mV) and distal area (mV.ms) i.e., amplitude or area of the CMAP on stimulation of the wrist or ankle, the proximal amplitude (mV) and proximal area (mV.ms) i.e., amplitude or area of the CMAP on stimulation of the

axilla or popliteal fossa, and the total amplitude reduction (mV) and total area reduction (mV.ms), calculated as distal minus proximal amplitude or area, were determined. Definite conduction block was defined as an area reduction P/D of at least 50%[68,181,231] and probable conduction block as an amplitude reduction P/D of at least 30% in an arm nerve.[2,66,231] Conduction block was only scored when the distal amplitude of the segment was at least 1 mV. Low CMAPs in a nerve were scored when the distal and proximal amplitude were below the lower limit of normal of our laboratory, i.e. below 3.5 mV for the median nerve, 2.8 mV for the ulnar nerve, and 2.5 mV for the peroneal nerve. If necessary, a collision technique was used to detect effects of co-stimulation.[115,223] EMGs were performed before the initial IVIg course (t = 0) and once a year (t = 1-8) during follow-up.

Statistical analysis

A paired t-test was used to compare mean MRC sumscores before and after the first full course of IVIg and before IVIg treatment and after the last follow-up examination. The functional impairment scores before and after the first full course of IVIg and the electrophysiological variables before and after follow-up were compared using the Wilcoxon's matched pairs test. A simple linear regression was used to evaluate the change in MRC sumscore and functional impairment score from after the first full course of IVIg until after the last follow-up examination and the slope for each patient was calculated. A t-test was used to evaluate the null hypothesis that the average of the slopes was not significantly different from zero. Subsequently, a multiple linear regression model was used to evaluate the effect of various baseline variables on the changes in slopes of the MRC sumscores. With a t-test we additionally evaluated whether the slope of the MRC sumscores in the group of patients with disease restricted to the upper limbs at the onset of treatment was significantly different from the group of patients with disease in both upper and lower limbs. A p-value < 0.05 was considered to be significant.

Results

Muscle Strength

At onset of treatment, weakness was restricted to the upper limbs in four patients. At the last follow-up examination weakness remained restricted to the upper limbs in two of these four patients. At onset of treatment only one patient had weakness in muscle groups innervated by one or two nerves; this patient had more widespread muscle weakness at the last follow-up examination. In contrast, two patients showed weakness in muscle groups innervated by more than two nerves at onset of

treatment but improved during IVIg maintenance treatment, such that at the last follow-up examination weakness was only found in muscle groups innervated by one or two nerves.

The MRC sumscores for each patient during IVIg maintenance treatment are shown in figure 1. The mean MRC sumscore of all patients was 92 (SD 7) before and 95 (SD 6) after the first full course of IVIg ($p < 0.001$). The mean MRC sumscore at the last follow-up examination was 94 (SD 7), which was also significantly

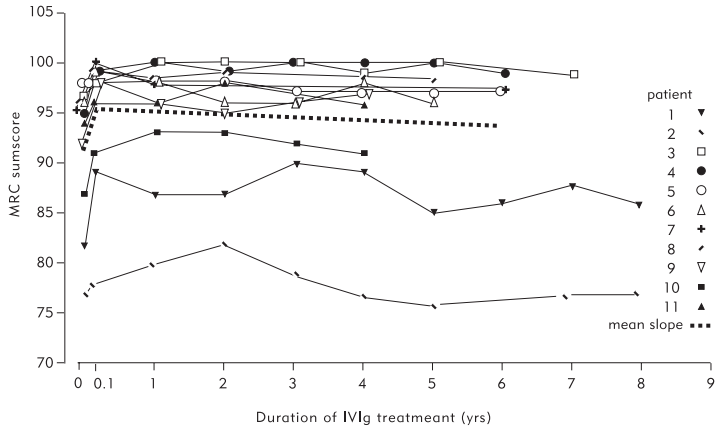

Figure 1. Muscle strength of 11 patients, expressed as MRC sumscores, during IVIg maintenance treatment. Horizontal axis: 0 = before the onset of IVIg treatment, 0.1 = after the first full course of IVIg, 1 - 8 = during and after follow-up.

higher than the mean MRC sumscore before the first full course of IVIg ($p < 0.001$). The average slope of the MRC sumscores from after the first full course of IVIg until the last follow-up examination was -0.2 (SD 0.2). Comparing this average slope with the values after the first full course of IVIg revealed a significant decline in MRC sumscore during follow-up ($p < 0.01$). A multiple linear regression model did not show any clinical or laboratory baseline variable to have influenced the average slope of the MRC sumscores. There was no significant difference in the slopes of the group of patients with weakness restricted to the upper limbs at onset of treatment and the group of patients with weakness in upper and lower limbs.

The results of hand-held dynamometry measured in those muscle groups whose strength improved or worsened ≥ 25% during follow-up are shown in table 2. It shows that in individual patients muscle strength either improved or worsened, and that only in patient 10 muscle strength did improve in some muscle groups and worsen in other muscle groups.

Table 2. Muscle strength (Newtons) measured by hand-held dynamometry in muscle groups with > 25% improvement or worsening during maintenance treatment

			Follow-up (years)								
Patient	*Muscle group*	*t =*	*0*	*0.1*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
1	Left wrist extension		100	135	75	120	NA	84	NA	62	101	62
	Right hand grip		75	75	70	75	NA	50	NA	54	50	59
2	Left shoulder abduction		45	80	160	160	160	153	220	NA	NA	185
	Left elbow extension		22	35	75	74	35	NA	55	NA	NA	57
	Right wrist extension		0	15	25	23	9	10	10	NA	NA	70
4	Left shoulder abduction		69	120	122	124	MRC5	141	189	MRC5		
	Left elbow flexion		46	101	111	118	MRC5	213	220	MRC5		
	Left wrist extension		21	95	99	84	90	169	187	140		
5	Left wrist extension		20	100	78	79	70	44	57	38		
	Left hand grip		21	45	54	57	82	28	61	38		
6	Right wrist extension		12	75	42	48	25	12	11			
	Left wrist extension		41	101	95	95	46	32	44			
8	Right wrist extension		0	40	NA	NA	NA	108				
9	Left shoulder abduction		120	235	MRC5	102	NA	173				
	Left elbow flexion		50	MRC5	110	106	97	144				
	Left wrist extension		50	130	100	87	63	139				
10	Right shoulder abduction		86	150	80	108	89	110				
	Left shoulder abduction		122	210	130	155	114	153				
	Right elbow flexion		10	60	93	151	148	153				
	Left ankle dorsiflexion		124	140	90	83	110	112				

NA = measurement not available. MRC5 = MRC score of 5 and dynamometry not performed.

Table 3. Electrophysiological findings before and after follow-up and changes during follow-up

Patient		Median nerve		Ulnar nerve		Peroneal nerve	
		Right	Left	Right	Left	Right	Left
1	Before	prob CB$^{lower\ arm}$	-	-	low CMAPs	-	-
	Change	a) ↑ all CMAPs + ↓ CMAP red$^{lower\ arm}$ b) ↓ all CMAPs + ↑ CMAP red$^{lower\ arm}$	-	↑ CMAP red$^{upper\ arm}$	-	-	-
	After	prob CB$^{lower\ arm}$	-	def CB$^{upper\ arm}$	low CMAPs	-	-
2	Before	low CMAPs	low CMAPs	low CMAPs	def CB$^{lower\ arm}$ + prob CB$^{upper\ arm}$	low CMAPs	low CMAPs
	Change	-	↑ CMAP red$^{lower\ arm}$	-	a) ↓ CMAP$^{wrist\ ,\ elbow}$; b) ↑ CMAP^{wrist}	-	-
	After	low CMAPs	low CMAPs + prob CB$^{lower\ arm}$	low CMAPs	prob CB$^{lower\ arm}$	low CMAPs	low CMAPs
3	Before	def CB$^{upper\ arm}$	-	-	-	-	-
	Change	↓ CMAP red$^{upper\ arm}$	↓ all CMAPs	-	-	↓ all CMAPs	-
	After	-	-	-	-	-	-
4	Before	-	prob CB$^{upper\ arm}$	-	def CB$^{upper\ arm}$	-	-
	Change	↑ CMAP$^{wrist\ ,\ elbow}$	↑ all CMAPs	↑ CMAP^{wrist}	↑ CMAP red$^{lower\ arm}$	-	-
	After	prob CB$^{upper\ arm}$	prob CB$^{upper\ arm}$	prob CB$^{lower\ arm}$	def CB$^{upper\ arm}$ + prob CBl$^{ower\ arm}$	-	-
5	Before	-	def CB$^{lower\ arm}$	-	-	-	-
	Change	↓ all CMAPs + ↑ CMAP red$^{upper\ arm}$	↓ CMAP red$^{lower\ arm}$	↓ all CMAPs	-	↓ all CMAPs	-
	After	prob CB$^{upper\ arm}$	-	-	-	-	-
6	Before	low CMAPs + def CB$^{lower\ arm}$	-	low CMAPs + def CB$^{lower\ arm}$	def CB$^{upper\ arm}$	-	-
	Change	↓ CMAP^{wrist}	↑ CMAP^{wrist}	-	-	-	↓ all CMAPs
	After	low CMAPs	prob CB$^{lower\ arm}$	low CMAPs + def CB$^{lower\ arm}$	def CB$^{upper\ arm}$	-	low CMAPs
7	Before	-	-	-	-	low CMAPs	-
	Change	-	-	-	↑ CMAP red$^{lower\ arm}$	-	↓ all CMAPs
	After	-	-	-	prob CB$^{lower\ arm}$	low CMAPs	-
8	Before	-	prob CB$^{lower\ arm}$	prob CB$^{upper\ arm}$	-	-	-
	Change	↑ all CMAPs	↓ CMAP red$^{lower\ arm}$	↓ CMAP red$^{upper\ arm}$	-	-	-
	After	-	-	-	-	-	-
9	Before	-	-	prob CB$^{lower\ arm}$	-	-	def CB$^{lower\ leg}$
	Change	↓ all CMAPs	-	-	-	-	-
	After	-	-	def CB$^{lower\ arm}$	-	-	def CB$^{lower\ leg}$
10	Before	low CMAPs	low CMAPs	def CB$^{lower\ arm}$	low CMAPs	low CMAPs	-
	Change	-	-	↓ CMAP red$^{lower\ arm}$	-	-	-
	After	low CMAPs	low CMAPs	prob CB$^{lower\ arm}$	low CMAPs	low CMAPs	-
11	Before	prob CB$^{lower\ arm}$	-	prob CB$^{lower\ arm}$	prob CB$^{lower\ arm}$	-	-
	Change	a) ↓ CMAP red$^{lower\ arm}$; b) ↓ all CMAPs	-	↑ all CMAPs	↑ all CMAPs	↓ all CMAPs	↑ all CMAPs
	After	prob CB$^{lower\ arm}$	-	prob CB$^{lower\ arm}$	prob CB$^{lower\ arm}$	-	-

Before: before IVIg treatment, after: at the last follow-up examination. Def CB = definite conduction block, prob CB = probable conduction block. Low CMAPs = compound muscle action potentials < lower limit of normal. a), b) = improvement followed by worsening or vice versa. The six types of change included: (1) ↑ all CMAPs = increase in the amplitude of all CMAPs. (2) ↓ all CMAPs = decrease in the amplitude of all CMAPs. (3) ↓ CMAP red = decrease in CMAP reduction P/D in the nerve segment (indicated by superscript) without change in the distal CMAP. (4) ↑ CMAP red = increase in CMAP reduction P/D in the nerve segment (indicated by superscript) without change in the distal CMAP. (5) ↑ CMAPwrist (or elbow) = increase in CMAP reduction P/D in a nerve segment due to increase in the distal CMAP. (6) ↓ CMAPwrist (or elbow) = decrease in CMAP reduction P/D in a nerve segment due to decrease in the distal CMAP.

Disability

The upper limb disability scores improved in seven patients and remained unchanged in four patients after the first full course of IVIg, a significant improvement ($p < 0.02$). The lower limb disability scores of three patients improved and in eight patients the lower limb disability score remained unchanged after the first full course of IVIg; this was not significant (table 1). The average slope of the upper limb disability scores from after the first full course of IVIg until the last follow-up examination was -0.1 (SD 0.8) and for the lower limb disability scores -0.4 (SD 0.7). Comparing these average slopes with the values after the first full course of IVIg revealed that the declines in upper and lower limb disability scores during follow-up were not significantly different from zero.

Electrophysiological studies

Before IVIg treatment conduction block was found in 18 nerve segments (seven median nerve segments, ten ulnar nerve segments, and one peroneal nerve segment) (table 3). Conduction block was still present in 12 of these segments (three median nerve segments, eight ulnar nerve segments and one peroneal nerve segment) at the last follow-up examination, and new conduction block was detected in eight nerve segments (four median nerve segments and four ulnar nerve segments). Before IVIg treatment, low CMAPs were found in 13 nerves (five median, four ulnar and four peroneal nerves). At the last follow-up examination, low CMAPs were still found in these 13 nerves and in addition in one peroneal nerve.

Changes of more than 2.0 mV in CMAP amplitude, or of more than 25% in amplitude reduction P/D or area reduction P/D[47] were scored to analyze changes in electrophysiological variables during IVIg maintenance treatment. These criteria are based upon intraobserver studies on CMAP amplitude and conduction block, performed by one of the authors (HF) in patients with MMN who were investigated several times with an interval of one week (unpublished). Six types of change during IVIg treatment were identified (see below) (table 3), and these changes were attributed to one or more pathophysiological mechanisms i.e. 'remyelination', 'reinnervation', 'demyelination', or 'axonal loss'. The six types of change included:

(1) Increase in the amplitude of all CMAPs. We attributed this to remyelination which restored conduction in previously blocked fibres distal to the wrist or ankle or to reinnervation either due to collateral sprouting or due to axonal regeneration (ingrowth of previously damaged axons along the basal lamina) in previously denervated motor units. This occurred in six nerves: three median nerves (patients 1, 4 and 8), two ulnar nerves (both in patient 11) and one peroneal nerve (patient 11).

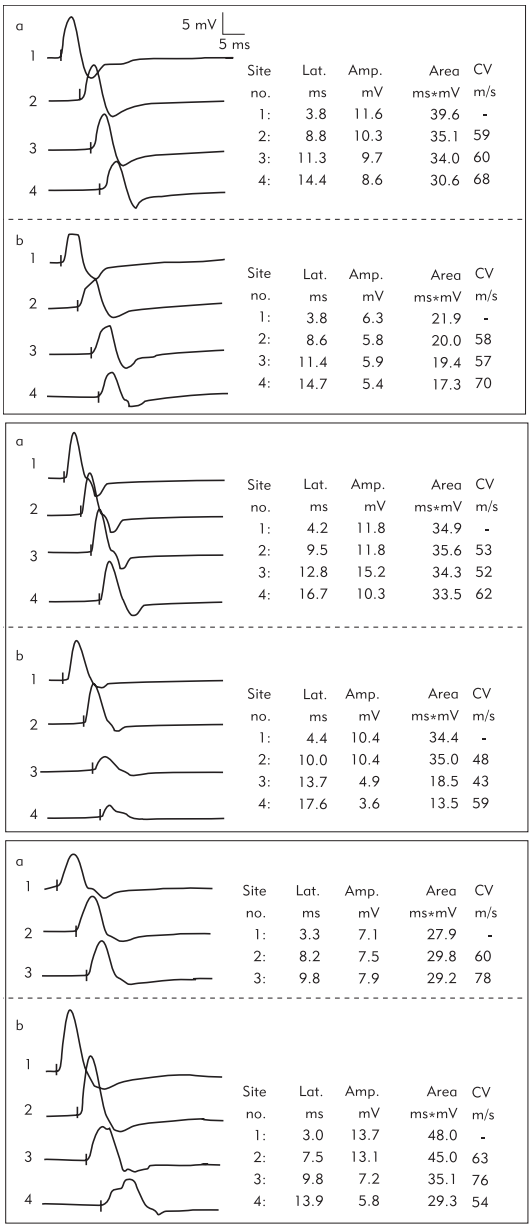

Figure 2. Comparisons between motor nerve conduction studies performed before IVIg treatment (a) and after follow-up (b) in patient 9 (upper), patient 5 (middle), and patient 4 (lower). For all patients the right median nerve was stimulated at the wrist (1), elbow (2), axilla (3), or Erb's point (4). In patient 9 no abnormalities were found before IVIg treatment; after follow-up there was a decrease in the amplitude of all CMAPs (change of type 2). In patient 5 no abnormalities were found before IVIg treatment but there was an increase in the CMAP reduction P/D in the upper arm segment without a change in the CMAPs evoked at the wrist and elbow (change of type 4) at the first follow-up examination (middle, b). After the second follow-up examination, all CMAPs had decreased (not shown). In patient 4 no abnormalities were found before IVIg treatment but there was an increase in the amplitude of the CMAPs evoked at the wrist and elbow without a change in the CMAPs evoked at the axilla and Erb's point at the last follow-up examination (change of type 5).

(2) Decrease in the amplitude of all CMAPs (figure 2, upper). We attributed this to distal demyelination yielding conduction block distal to the wrist or ankle or to axonal loss. This was seen in 11 nerves: five median nerves (patients 1, 3, 5, 9 and 11), one ulnar nerve (patient 5) and five peroneal nerves (patients 3, 5, 6, 7 and 11).
(3) Decrease in CMAP reduction P/D in a nerve segment without change in the distal CMAP. We attributed this to remyelination of the nerve segment which either restored conduction in previously blocked nerve fibres or decreased temporal dispersion. This was seen in seven nerves: five median nerves (patients 1, 3, 5, 8 and 11) and two ulnar nerves (patients 8 and 10).
(4) Increase in CMAP reduction P/D in a nerve segment without change in the distal CMAP (figure 2, middle). We attributed this to demyelination of the nerve segment which either yielded conduction block or increased temporal dispersion. This was seen in six nerves: three median nerves (patients 1, 2 and 5) and three ulnar nerves (patients 1, 4 and 7).
(5) Increase in CMAP reduction P/D in a nerve segment due to increase in the distal CMAP; the CMAP reduction P/D now fulfilled criteria for CB (figure 2, lower). We attributed this to distal remyelination which restored conduction in previously blocked nerve fibres, which in turn resulted in the appearance of conduction block in a more proximal segment, or to reinnervation due to axonal regeneration but not to collateral sprouting of previously denervated motor units. This occurred in four nerves: in the lower arm segment of one median nerve (patient 6), in the upper arm segment of one median nerve (patient 4) and in the lower arm segment of two ulnar nerves (patient 2 and 4).
(6) Decrease in CMAP reduction P/D in a nerve segment due to decrease in the distal CMAP; the CMAP reduction P/D no longer fulfilled criteria for CB. We attributed this to distal demyelination which yielded distal conduction block or to axonal loss in previously blocked nerve fibres. This was seen in two nerves: in the lower arm segment of one median nerve (patient 6) and in the upper arm segment of one ulnar nerve (patient 2).

Changes consistent with improvement ('remyelination' or 'reinnervation', i.e. type of change 1, 3 or 5) occurred in 13 nerves and changes consistent with worsening ('demyelination' or 'axonal loss', i.e. type of change 2, 4 or 6) occurred in 14 nerves during the follow-up period. In one of the nerves (table 3; median nerve of patient 5) two sequential changes were observed, both implying worsening. In three nerves two to four changes per nerve were observed, implying improvement followed by worsening (table 3; median nerve of patients 1 and 11) or worsening followed by improvement (table 3; ulnar nerve of patient 2); these nerves were not scored as showing improvement or worsening. In 36 of the 66 investigated nerves no changes

were observed. Improvement was significantly associated with the presence of conduction block before IVIg treatment: eight of the 13 nerves that improved during follow-up had conduction block before IVIg treatment, whereas only two of the 14 nerves that worsened during follow-up had conduction block before IVIg treatment ($p < 0.02$).

In the 17 nerves with conduction block before IVIg treatment, the mean distal and proximal amplitude and area were higher and the mean total amplitude and area reduction were lower at the last follow-up examination than before treatment (table 4). This was significant for the proximal amplitude and area. In contrast, in

Table 4. Comparison of mean values (SD) of electrophysiological variables before and after follow-up

	Before follow-up	*After follow-up*	*P*
Nerves with conduction block at EMG before treatment			
Distal amplitude (mV)	6.1 (2.2)	6.7 (3.0)	NS
Distal area (mV.ms)	18.4 (7.6)	19.9 (10.6)	NS
Proximal amplitude (mV)	2.0 (1.3)	3.3 (2.4)	< 0.01
Proximal area (mV.ms)	7.3 (6.0)	13.6 (10.1)	< 0.01
Total amplitude reduction (mV)	4.1 (1.6)	3.6 (2.2)	NS
Total area reduction (mV.ms)	10.3 (5.7)	6.7 (6.3)	NS
Nerves without conduction block at EMG before treatment or during follow-up			
Distal amplitude (mV)	6.5 (5.0)	6.2 (4.6)	NS
Distal area (mV.ms)	22.0 (15.1)	19.3 (14.1)	< 0.05
Proximal amplitude (mV)	5.8 (4.3)	5.5 (4.0)	< 0.05
Proximal area (mV.ms)	20.6 (13.8)	18.3 (13.5)	< 0.05
Total amplitude reduction (mV)	1.1 (1.2)	1.3 (1.8)	NS
Total area reduction (mV.ms)	1.9 (2.5)	2.0 (3.2)	NS

SD = standard deviation. NS = not significant.

the 42 nerves in which no conduction block was demonstrated before IVIg treatment or after follow-up, the mean distal and proximal amplitude and area were lower, and the total amplitude and area reduction were higher after follow-up than before IVIg treatment. This was significant for the distal area and the proximal amplitude and area.

Adverse effects

In all patients IVIg maintenance treatment was well tolerated over the years and the previously described side effects (headache, rash, fatigue)[224-226] only caused minor inconvenience.

Discussion

In this study of 11 patients with MMN who were treated with IVIg maintenance treatment for 4 to 8 years, we found that muscle strength and upper limb disability scores were significantly better at the last follow-up examination than before IVIg treatment. During IVIg maintenance treatment, however, a slight, but statistically significant, decrease in MRC sumscores was observed. In individual muscle groups strength improved or deteriorated during the follow-up period. This is consistent with the electrophysiological changes which showed evidence of improvement (remyelination or reinnervation) predominantly in nerves with conduction block before treatment, but also evidence of deterioration (demyelination or axonal loss) predominantly in nerves in which no conduction block was found either before treatment or during the follow-up period.

Only two previous studies have described the long-term effect of IVIg maintenance treatment in patients with MMN, but the follow-up in these studies was less than four years. In a previous study we reported on seven patients who were on IVIg maintenance treatment for 2-4 years.[225] In the present study, we included five new patients, the follow-up was substantially longer, and the electrophysiological changes during follow-up were analyzed in greater detail. In another study, 12 out of 18 patients with MMN responded to repeated IVIg infusions.[9] In contrast to our study, no electrophysiological follow-up was performed. All 12 patients showed an improvement in muscle strength of at least 30% after 9 to 48 months. In most of these patients long-term IVIg maintenance treatment was necessary to sustain the improvement in muscle strength. However, in two patients treatment could be withdrawn after intermittent IVIg treatment for several months because both patients showed no deterioration after a follow-up of one year. Only one of our patients reported in our previous study has been in remission for five years after only two IVIg courses. This patient was not included in the present study as he no longer receives IVIg maintenance treatment.

Although remission of MMN, unlike chronic inflammatory demyelinating polyneuropathy, is very uncommon, a thorough evaluation of the effect of the first course of IVIg treatment is important before expensive and burdensome IVIg maintenance treatment is started. In none of the patients of the present study was remission induced by long-term IVIg maintenance treatment because discontinuation of IVIg maintenance treatment led to a deterioration of muscle strength. In another long-term study, six patients were treated with IVIg maintenance treatment in combination with oral cyclophosphamide such that the interval between IVIg infusions could be prolonged and IVIg treatment could be stopped in some patients.[146] After a mean follow-up period of 47 months, the MRC sumscore, Rankin disability scale,

and upper and lower limb impairment scores were significantly improved. However, cyclophosphamide was eventually stopped in most patients because of adverse effects (E. Nobile-Orazio, personal communication). Interestingly, in this study one patient developed weakness in muscle groups that were not affected before IVIg treatment was started. Deterioration of muscle strength during IVIg maintenance treatment was also observed in eight muscle groups of our patients. As we tailored the regimen of IVIg maintenance treatment on the basis of functioning in daily life and not primarily on the measurements of muscle strength, we cannot exlude the possibility that deterioration of muscle strength is due to the progression of disease or merely represents an insufficient IVIg maintenance treatment regimen. Due to the high cost of IVIg, it seems rational to increase dosage or frequency of IVIg infusions only when a patient is noticing deterioriation of functioning in daily life.

A decrease in conduction block during IVIg therapy has been reported in several studies[28,34,62,132,155,226], but long-term electrophysiological follow-up studies of patients with MMN are rare.[146,225] Meucci et al. reported a significant improvement of conduction block during treatment in 15 of 60 nerves, and new conduction block was found in one nerve.[146] Our electrophysiological studies revealed significant changes during the follow-up period. It is unlikely that these changes were due to intraobserver variation or fluctuations in temperature as the criteria for CMAP amplitude changes were based on our own intraobserver studies and nerves were warmed in water at 37°C for at least 30 minutes before each EMG. Histopathological studies of MMN revealed demyelination, small onion bulbs indicative of poor remyelination, axonal damage, and regenerative clusters indicative of axonal regeneration.[35,106] Conduction block in MMN is most likely due to demyelination but blocking of sodium channels at the axolemma of the node of Ranvier[210] cannot be fully excluded despite the failure to induce sodium channel blocking by short-term application of anti-GM1 antibodies.[90] The presence of muscle atrophy and signs of denervation and collateral sprouting on concentric needle examination that have been found in patients with MMN, are also indicative of axon involvement.[169,213] Although it is based upon investigations in a few patients, the above described evidence suggests that remyelination, demyelination, axonal regeneration, collateral sprouting and axon loss all occur in patients with MMN. At present, the effects of these mechanisms can be estimated only by repeated electrophysiological investigation. For these reasons, we tried to explain the electrophysiological changes in terms of these mechanisms. However, the relative contribution of these mechanisms is not known. In our present study, 18 nerve segments had conduction block before IVIg treatment; in six segments the conduction block disappeared during the follow-up period. Although this suggests that IVIg treatment

induces remyelination, new conduction block developed in four nerve segments during the follow-up period. In four other nerves conduction block appeared during treatment, together with an increase in distal amplitude (change of type 5). It is possible that the latter does not represent new conduction block but merely unmasking of previously undetected conduction block in a more proximal segment due to remyelination distal to the wrist.[23] Although these findings suggest a rather limited effect of IVIg treatment, the significant increase in the proximal CMAP amplitude and area in nerves with conduction block before IVIg treatment implies that in these nerves IVIg treatment favourably influenced mechanisms of remyelination. In contrast, in those nerves in which conduction block was found neither before treatment nor during follow-up, there was a significant decrease in distal CMAP area and proximal CMAP amplitude and area. This can be explained by demyelination yielding conduction block distal to the wrist or ankle but also by axonal loss. An increase in CMAP reduction yielding conduction block in the much longer lower arm or upper arm segments, was found in only four nerves without conduction block during the follow-up period. As demyelination probably occurs randomly over the whole length of a nerve (H. Franssen, unpublished observation), axonal loss is more likely to occur than is the development of distal conduction block. Our findings therefore suggest that in MMN axonal loss occurs despite IVIg treatment.

Although IVIg maintenance treatment does not prevent a mild global decrease in muscle strength and does not induce remission of MMN, we found that IVIg maintenance treatment had a beneficial long-term effect on muscle strength, upper limb disability, and electrophysiological variables in nerves with conduction block and that treatment was well tolerated. As there is currently no acceptable alternative treatment, IVIg maintenance treatment is indicated in patients with MMN, although the high cost of IVIg maintenance treatment is a strain on hospital budgets and is the subject of many discussions with insurance companies. The number of IVIg infusions that are necessary to maintain an acceptable level of functioning varies per patient and thus treatment needs to be individually tailored. The (side) effects of IVIg treatment in combination with immunosuppressive drugs that are less toxic than cyclophosphamide need to be investigated in future studies of the long-term treatment of patients with MMN.

Treatment of multifocal motor neuropathy with interferon-β1a

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Introduction

Multifocal motor neuropathy (MMN) is characterized by slowly progressive, predominantly distal, asymmetrical weakness, and muscular atrophy of the limbs without sensory loss. Evidence of motor conduction block on electrophysiological examination differentiates MMN from motor neuron disease (MND). Several studies have found evidence for an immune-mediated pathogenesis of MMN[26,117,131,153,171,243], leading to studies of several immunological treatments in MMN. Prednisolone and plasma exchange are ineffective in most patients, and of the immunosuppressants only cyclophosphamide seemed to be effective but has major side-effects.[10,143,173] In various studies, treatment with high-dose intravenous immunoglobulins (IVIg) has been shown to improve muscle strength in patients with MMN.[8,28,155,224,226] However, as the effect of IVIg in MMN usually lasts several weeks only, maintenance treatment is expensive. Moreover, the frequent infusions may be burdensome for the patient.
Multiple sclerosis (MS) is an immunological demyelinating disease of the central nervous system and, similar to MMN, characterized by multifocal inflammatory lesions. The interferons beta-1a and 1b are effective for the relapsing-remitting[55,97,186,203] and secondary progressive forms of MS.[108] Recently, a favorable effect of IVIg in relapsing-remitting MS has been reported.[60] These findings prompt the hypothesis that interferon beta, as in MS, may also be effective in MMN. Recent findings of improvement after interferon-beta-1a (IFN-β1a) treatment in patients with chronic motor neuropathies, not responding to conventional therapies such as IVIg, cyclophosphamide, steroids, or plasma exchange, support this hypothesis.[135] In the present study, we investigated whether IFN-β1a treatment would result in improvement in muscle strength or disability in patients with MMN, who had improved after treatment with IVIg.

Patients and methods

Objectives of the study

The objectives of the study were to investigate whether improvement in muscle strength and disability in patients with MMN can be achieved by IFN-β1a treatment. We compared the effects of IFN-β1a treatment on muscle strength with that of IVIg. Furthermore, we tested the safety of IFN-β1a treatment in patients with MMN.

Patients

Included in the study were nine patients who (1) were diagnosed as having MMN based on the presence of progressive asymmetrical weakness and atrophy without sensory involvement or upper motor neuron signs, and with electrophysiological evidence of motor conduction block, and (2) had shown a beneficial response to IVIg treatment according to criteria used in previous studies.[224,226] The clinical and laboratory features of the nine patients are described in table 1. The age at onset of disease ranged from 24 to 47 years. Four patients (patients 1-4) had received one or two full courses of IVIg (0.4 g/kg for 5 consecutive days) before the onset of IFN-β1a treatment, and five patients (patients 5-9) received IVIg maintenance treatment (16-30 g every week) over a period of 2 to 6 years which was stopped before IFN-β1a treatment was started.[225] The study was approved by the medical ethics committee of our hospital and was carried out between March 1998 and June 1999. All patients gave informed consent. None of the patients was treated with any other immunological therapy prior to onset of the study.

Study design

In this open study, the patients were treated with IFN-β1a (Rebif®, Serono Benelux) subcutaneously in increasing doses of 1.2 million units (4.4 μg), three times in the first week, 3.0 million units (11 μg), three times in the second week, and 6.0 million units (22 μg), three times a week for a period of six months.[55]

In patients 1-4, IFN-β1a treatment was initiated at the time when muscle strength had returned to the level before the last treatment course with IVIg. In patients 5-9, IVIg maintenance treatment was stopped one week prior to onset of IFN-β1a treatment. In patients 5-9 we took into account the possibility that the onset of a potential effect of IFN-β1a could take several weeks of treatment[31,135], and that deterioration in muscle strength during the first weeks of the study could occur due to discontinuation of IVIg treatment. To avoid unacceptable deterioration of functioning in daily life, compared to that during IVIg maintenance treatment, we stated that patients 5-9 would receive 'rescue' therapy consisting of an infusion of IVIg (0.4 g/kg) during IFN-β1a treatment if the MRC sumscore (range 0-100; see assessment of treatment response) declined by at least three points. Another infusion of IVIg could be administered if deterioration recurred.

Prior to the study, ECG, chest X-ray and laboratory investigations (routine hematology, blood biochemistry, pregnancy test, and urine-analysis) were performed. During the study, routine hematology, liver function and urine-analysis were monitored every three weeks. Anti-GM1 antibodies were measured before IFN-β1a treatment.[228]

Table 1. Clinical and laboratory features and treatment response in nine patients

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*	*Patient 8*	*Patient 9*
Clinical features									
Sex	Male	Female	Male	Male	Male	Male	Male	Male	Male
Age at onset (years)	41	25	24	25	47	43	30	41	40
Disease duration (years)	11	1	6	4	11	11	8	12	8
Site of onset	left foot	left hand	right hand	right foot	right arm	right foot	left hand	left hand	left arm
Currently affected sites	both arms left foot	both arms left foot	right arm	both hands both feet	both arms left foot	both hands both feet	left arm	both arms	both arms both legs
Laboratory features									
CSF protein (mg/dl)	38	43	25	56	65	-	73	54	76
Anti-GM1 antibodies	positive	negative	negative	positive	negative	-	negative	negative	negative
Treatment									
Duration of IVIg maintenance treatment (yrs)	no	no	no	no	6	4	4	4	2
Dosage IVIg before IFN-β1a (g/week)	-	-	-	-	24	16	28	30	15
IVIg dose given during study (g/week)	no	no	no	no	no	13	7	21	15
Response on IFN-β1a*	responder	responder	responder	non-responder	non-responder	non-responder	non-responder	non-responder	non-responder
Rankin before IFN-β1a	2	1	1	2	3	2	1	0	1
Rankin after discontinuation IFN-β1a	2	1	1	2	3	2	2	0	1

*- = not applicable. * = measured by hand-held dynamometry; for definition see Methods. Rankin= modified Rankin-scale.*

Assessment of treatment response

The clinical response was monitored every three weeks by assessing muscle strength and disability. All measurements were done by the same examiner (R.v.d.B-V). The measurements of muscle strength were continued until at least six months after discontinuation of IFN-β1a.

Muscle strength was measured by hand-held dynamometry[235] in clinically weak muscles (Medical Research Council (MRC) scale < 5), bilaterally in six proximal muscle groups (arm abduction, elbow flexion, elbow extension, hip flexion, knee extension and knee flexion) and four distal muscle groups (wrist extension, wrist flexion, ankle dorsiflexion and ankle plantarflexion). Grip strength of the hands was measured only using a hand-held dynamometer. The values obtained by hand-held dynamometry (in Newtons) were divided by the 5th centile (P5) values for the muscle strength of normal adults of the same sex for that muscle, and multiplied by 100 to obtain a percentage of normal.[235] These results were used to assess the clinical response similar to our previous studies[225,226] : a patient was defined as a 'responder' when muscle strength or grip strength improved by 50% or more in at least two clinically affected muscles or muscle groups, without a decrease of 25% or more in muscle strength or grip strength in more than one muscle or muscle group. 'Non-responders' were the patients who did not respond according to the above-mentioned criteria. Subsequently, the values of the affected proximal and distal muscle groups in arms and legs, respectively, were determined by deriving the average of the data for individual muscle groups.[176,225] In addition, a total MRC sumscore was calculated of the six proximal and four distal muscle groups, which was maximal at 100. When 'rescue' therapy was given, we used the MRC sumscore before the additional IVIg treatment as a parameter for the degree of being clinically affected instead of the MRC sumscore at the start of the study.

Disability was assessed using three different modalities: the nine hole peg test to test manual dexterity[136], the 10 meter walking test to evaluate ambulation, and the modified Rankin scale.[155,238] The modified Rankin scale was scored as follows: 0= asymptomatic; 1= non-disabling symptoms not interfering with lifestyle; 2= minor disability leading to some restriction of lifestyle but not interfering with patients' capacity to look after themselves; 3= moderate disability with symptoms significantly interfering with lifestyle or preventing totally independent existence; 4= moderately severe disability with symptoms preventing independent existence, although patients do not need constant attention day and night; 5= severely disabled, totally dependent, requiring constant attention day and night.

Electrophysiological studies

Motor nerve conduction was studied with surface electrode electroneurography (ENG) before (ENG I) and after (ENG II) treatment, by one investigator (HF). We carried out bilateral investigations of the lower arm-, upper arm-, shoulder- (i.e., between axilla and Erb's point) and lower leg segments of the median (recording from the m. abductor pollicis brevis and m. flexor carpi radialis), ulnar (recording from the m. abductor digiti V), radial (recording from the m. extensor carpi ulnaris), musculocutaneous (recording from the m. biceps brachii), deep peroneal (recording from the m. extensorum digitorum brevis), and tibial (recording from the m. abductor hallucis) nerves. Prior to an investigation, the arms and legs were warmed in water at 37° C for 30 minutes; during the investigation the extremities were kept warm by infrared heaters.[67] From each compound muscle action potential (CMAP) we determined the amplitude and area of the negative part. We expressed the CMAP reduction on proximal versus distal stimulation not only in percentages but also in mV as the latter offers a more realistic indication of conduction abnormalities, especially when the distal CMAP amplitude is low.

For each nerve segment we determined: segmental amplitude reduction (%) and segmental area reduction (%), calculated as (CMAP on distal stimulation of the segment - CMAP on proximal stimulation of the segment)100% / CMAP on distal stimulation of the segment, to estimate the combined effects of conduction block and temporal dispersion in a nerve segment. For each nerve we determined: distal amplitude (mV) i.e., amplitude of the CMAP on stimulation of the most distal site of the nerve, to estimate the combined effects of axonal loss and distal conduction block, proximal amplitude (mV) i.e., amplitude of the CMAP on stimulation of the most proximal site of the nerve, to estimate the combined effects of conduction block, temporal dispersion and axonal loss along the entire length of the nerve studied, and total amplitude reduction (mV) i.e., distal amplitude - proximal amplitude, to estimate the combined effects of conduction block and temporal dispersion along the entire length of the nerve studied. For each patient we determined: mean distal amplitude (mV), mean proximal amplitude (mV), mean total amplitude reduction (mV) of all nerves studied, the number and percentage of segments with definite conduction block (segmental area reduction of at least 50%) or probable conduction block (segmental amplitude reduction in an arm nerve of at least 30%).[2,66,68,181] The change in a variable between ENG I and ENG II was calculated as value at ENG II - value at ENG I. For each nerve segment or nerve, improvement or worsening was defined as a change in segmental amplitude reduction of at least 20% or a change in total amplitude reduction of at least 2 mV.

Conduction block was only considered when the CMAP amplitude on distal stimulation of a nerve segment was at least 1 mV. When the CMAP amplitude on stimu-

lation of the axilla was below 1 mV we did not stimulate at Erb's point. For these reasons and because patient 8 refused stimulation at Erb's point at ENG II, the number of nerve segments analyzed was not equal in all patients.

Statistical analysis

The Mann-Whitney U test was used to compare clinical characteristics and electrophysiological variables between the group of responders and the non-responders. The electrophysiological variables before and after treatment were compared using the Wilcoxon's matched pairs test. A p-value < 0.05 was considered to be significant.

Results

Treatment response

Patients 1-3 improved in muscle strength on IFN-β1a treatment according to the above mentioned criteria (responders). The onset of improvement occurred after seven weeks in patient 1 and after six weeks in patients 2 and 3. The hand-held dynamometry results of the muscle groups that improved by 50% or more are shown in table 2. In 9 of the 12 improved muscle groups the muscle strength on IFN-β1a treatment was greater than on IVIg. In addition, the response of patient 2 to treatment is shown in figure 1. The improvement on hand-held dynamometry was in agreement with the subjective judgement of the patients: patient 1 noticed gradual improvement in dexterity of the right hand in such a way that he could better perform his work as a technician; in patient 2 walking became easier and dexter-

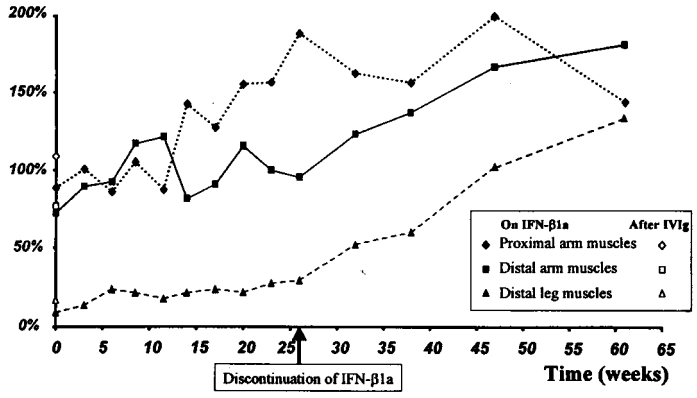

Figure 1. Percentages of muscle strength of patient 2.

Table 2. Muscle strength (Newtons) in muscle groups with > 50% improvement during IFN-β1a treatment measured by hand-held dynamometer in three responders

	Maximum after IVIg	*Start IFN-β1a*	*After three months*	*After six months**	*Last measurement*
Patient 1					
Right wrist extension	70	30	35	**62**	**63**
Right hand grip	62	57	63	78	**86**
Left hand grip	84	52	77	**79**	76
Left ankle dorsiflexion	60	20	16	**32**	**56**
Left ankle plantarflexion	210	150	182	212	**252**
Patient 2					
Right arm abduction	78	77	93	**143**	110
Left arm abduction	85	56	**121**	**120**	**112**
Right hand grip	48	47	53	62	**116**
Left ankle dorsiflexion	26	15	**35**	**48**	**217**
Patient 3					
Right elbow extension	135	79	**140**	**119**	**125**
Right wrist extension	55	31	**70**	**80**	**85**
Right hand grip	21	11	14	**23**	**20**

** = discontinuation of IFN-β1a. Bold numbers represent values of muscle groups that showed an improvement of >50% in strength compared with values before starting IFN-β1a.*

ity of the right hand improved; in patient 3 hand skills improved noticeably during various activities of daily life. In the three patients, improvement in muscle strength sustained itself, respectively, 27, 36 and 27 weeks after discontinuation of IFN-β1a treatment.

Patients 4-9 did not improve on IFN-β1a treatment according to the above-mentioned criteria (non-responders). Patient 5 who received maintenance therapy with IVIg before the study, remained stable under IFN-β1a. Patients 6-9 who also received maintenance IVIg treatment before the start of the study, deteriorated by at least three points (range 3 to 13) in their MRC sumscores (not shown). As a consequence, each received 'rescue' therapy consisting of several infusions of IVIg during the study (table 1). The mean maintenance dose of IVIg during the study was lower in patients 6, 7 and 8 and equal in patient 9 in comparison to the dose before the start of the study (table 1). For patient 7, however, this lower IVIg dose resulted in clinical deterioration. After discontinuation of IFN-β1a treatment all four patients returned to their former maintenance dose of IVIg.

At the level of disability, no substantial changes occurred in the nine hole peg test and the 10 meter walking test during treatment in either the group of responders or non-responders (not shown). The modified Rankin scale before and after the study was unchanged (table 1) in the responders and in the non-responders, with the exception of patient 7 who deteriorated one point on the modified Rankin scale and whose muscle strength also declined (not shown).

The following differences were found between responders and non-responders. The mean disease duration in the responders (6 years) was shorter than in the non-responders (9 years) (Mann-Whitney U test, not significant). Muscle strength was less impaired in the responders than in the non-responders: mean minimal MRC sumscore 96 versus 90 (Mann-Whitney U test, $p<0.025$) (table 1).

Adverse effects

Three patients reported flu-like symptoms and three patients reported headache after injection which responded well to paracetamol and gradually disappeared within a matter of weeks. Skin reactions at the injection-sites, consisting of local erythema and tenderness, were noticed by all patients and gradually lessened over a period of months. These local injection-site reactions and the fact that IFN-β1a treatment did not seem very successful were reasons to stop treatment prematurely in patient 6 after 14 weeks, and in patient 8 after 23 weeks. In patient 7, pain in the chest and dyspnea occurred; lung embolism was diagnosed. We attributed this to thrombosis of the adjacent vein to the intravenous access system which was not flushed with heparin solution as frequently under IFN-β1a treatment as under the weekly doses of IVIg. The patient was treated with anti-coagulantia and IFN-β1a treatment was

Table 3. Individual motor nerve conduction data.

	Mean distal amplitude (mV)		*Mean proximal amplitude (mV)*		*Number* of segments with definite condition block*		*Number* of segments with possible conduction block*		*Number** of segments with conduction block at ENG I and segmental amplitude reduction*		*Number** of nerves with total amplitude reduction at ENG I*	
Patient	*ENG I*	*ENG II*	*ENG I*	*ENG II*	*ENG I*	*ENG II*	*ENG I*	*ENG II*	*Improved*	*Worsened*	*Improved*	*Worsened*
1	7.8 (5.3)	7.3 (5.2)	6.1 (4.5)	5.3 (4.5)	1/24	1/24	3/24	2/24	0/4	2/4	1/12	1/12
2	10.3 (4.0)	10.8 (4.3)	8.6 (3.8)	9.0 (4.0)	1/25	1/26	0/25	1/26	1/1	0/1	1/13	0/13
3	8.7 (4.8)	8.0 (4.8)	8.5 (4.0)	7.5 (4.6)	1/24	1/25	1/24	1/25	0/2	0/2	1/12	0/12
4	6.0 (4.2)	6.7 (4.5)	4.3 (2.8)	5.1 (3.6)	1/26	0/26	3/26	4/26	0/4	0/4	0/14	1/14
5	5.9 (3.5)	6.0 (2.2)	2.9 (2.8)	2.3 (2.4)	6/26	11/25	5/26	2/25	1/10	1/10	1/13	3/13
6	4.4 (3.3)	5.8 (3.8)	1.7 (2.0)	3.8 (3.9)	6/21	6/23	3/21	3/23	3/9	1/9	2/8	0/8
7	9.8 (2.5)	9.3 (2.2)	5.2 (3.6)	5.6 (3.3)	4/26	3/26	3/26	4/26	2/7	0/7	4/14	0/14
8	7.5 (2.8)	6.8 (3.2)	4.8 (2.4)	4.4 (2.0)	1/15	2/16	5/15	4/16	0/6	1/6	0/11	0/11
9	6.6 (2.0)	6.9 (2.5)	3.5 (1.7)	4.6 (2.7)	2/26	2/26	4/26	1/26	3/6	0/6	2/14	0/14
Total					23/213	27/217	27/213	22/217	10/49	5/49	12/111	5/111

** = Relative to the total number of investigated segments in one patient.** = Relative to the number of segments or nerves that could be compared between ENG I and ENG II.*

not discontinued. Routine laboratory investigations revealed no significant abnormalities during the study.

Electrophysiological studies

We found no statistical differences between ENG I and ENG II for the values of mean distal amplitude and mean proximal amplitude (Wilcoxon's matched pairs test for each of the seven nerves, not significant). Definite conduction block or probable conduction block was found in 50 segments at ENG I and 49 segments at ENG II (table 3). In some segments or nerves, the segmental amplitude reduction or total amplitude reduction improved or worsened, but improvement was found more often than worsening (table 3). In patients 6 and 9 differences between ENG I and ENG II were found for the mean distal amplitude, mean proximal amplitude or the number of nerve segments with conduction block; these differences consisted of improvement at ENG II compared to ENG I. All these findings indicate that no important changes in axonal degeneration, conduction block or temporal dispersion occurred during treatment with IFN-β1a.

To assess whether responders differed from non-responders before the start of the study, we compared features of ENG I between the two groups (table 4). This

Table 4. Total mean and SD (in parentheses) of variables on ENG I in responders and non-responders

	Responders	*Non-responders*	*p**
Percentage of segments with definite CB	4.1 (0.0)	14.2 (9.9)	$p < 0.05$
Percentage of segments with probable CB	5.6 (6.4)	17.6 (8.2)	ns
Total mean of mean distal amplitude (mV)	8.9 (1.3)	6.7 (1.8)	ns
Total mean of mean proximal amplitude (mV)	7.7 (1.4)	3.7 (1.3)	$p < 0.025$
Total mean of mean total amplitude reduction (mV)	1.9 (0.4)	3.0 (1.1)	ns

** = Mann Whitney U-test. CB = conduction block. ns = not significant.*

revealed that responders had considerably fewer segments with conduction block (Mann-Whitney U test for definite conduction block $p < 0.05$, for possible conduction block not significant), considerably larger mean proximal amplitude (Mann-Whitney U test, $p< 0.025$), and slightly lower mean total amplitude reduction (Mann-Whitney U-test, not significant), all indicating that responders had less con-

duction block and temporal dispersion than non-responders. In responders, the mean distal amplitude was slightly larger than in non-responders (Mann-Whitney U test, not significant), indicating that responders had slightly less axonal degeneration or distal conduction block. Similar differences between responders and non-responders were found at ENG II (not shown).
There was no evidence that motor conduction variables improved more in responders than in non-responders (table 3). Because proximal and distal muscle groups were tested clinically, we performed a separate analysis of improvement or worsening of the segmental amplitude reduction and total amplitude reduction of CMAPs recorded from the proximal muscles (m. flexor carpi radialis, m. extensor carpi ulnaris and m. biceps brachii). This analysis did not reveal differences between responders and non-responders.

Discussion

IFN-β1a treatment resulted in improvement of muscle strength in three of the nine patients with MMN. This improvement occurred after at least six weeks of treatment and the effect remained present for months after discontinuation. The improvement in these three patients was more pronounced on IFN-β1a treatment than after one course of IVIg. A beneficial effect of IFN-β1a treatment has been reported previously in a case report of one CIDP patient[31] and in a study of three patients with MMN and one with pure motor CIDP.[135] A common factor in these patients was that they did not respond to various immunological treatments including IVIg, which is in contrast with our patients who all showed a beneficial response to IVIg. In the study by Martina et al., the most substantial effect of IFN-β1a treatment was observed in the patient who was the least affected as far as muscle strength and the extent of atrophy were concerned. This is in accordance with our results: in comparison with the non-responders, the responders had a shorter mean disease duration, had less impaired muscle strength and showed less sites with conduction block or increased temporal dispersion at the onset of IFN-β1a treatment. The electrophysiological findings in the group of responders suggest that electrophysiological studies may be helpful in identifying potential responders to IFN-β1a therapy. It is unlikely that the improvement of the three patients was due to a spontaneous remission of the disease, as the course of MMN is slowly or stepwise progressive in most patients[28,155,225,226] and remissions have not been reported.
Five patients (5-9) of the six who did not respond to IFN-β1a treatment received IVIg long-term maintenance treatment before the onset of the study. Therefore, it cannot be ruled out that, in these patients, IVIg interfered with IFN-β1a treatment.

This did not account for patient 4, who did not receive IVIg maintenance treatment prior to the study and who also did not respond to IFN-β1a treatment. Four of these six patients (6-9) required IVIg in addition to IFN-β1a treatment, according to the previously defined criteria of a deterioration of at least three points on the MRC sumscore. Despite IFN-β1a treatment, it was not possible to discontinue IVIg treatment in these patients during the follow-up period. If the effect of IFN-β1a had been similar to the effect of IVIg, it would have been possible to stop the additional IVIg completely. However, the fact that the mean maintenance dose of IVIg during IFN-β1a treatment was lower than on IVIg maintenance treatment alone, may suggest some effect of IFN-β1a in these patients.

Despite extensive electrophysiological measurements before and after IFN-β1a treatment, a clear association between clinical and electrophysiological improvement was not found. A poor association was found in previous studies on IVIg treatment in MMN.[29,34,225] Several explanations for this discrepancy can be put forward. First of all, conduction can be restored only in proximal nerve segments that are not easily accessible to electrophysiological measurements. Secondly, muscle strength is usually assessed from proximal muscles, whereas CMAPs are usually recorded from hand or foot muscles. For this reason we also recorded CMAPs from lower and upper arm muscles. Separate analysis of these data, however, failed to show an association between clinical and electrophysiological improvement. Thirdly, on the basis of computer simulations[181] and the influence of temperature[68], a reduction in CMAP area of at least 50% or 60% (proximal versus distal) is required for the diagnosis of conduction block. Thus, moderate CMAP reductions on proximal versus distal stimulation are more likely to be the result of increased temporal dispersion than conduction block. Therefore, we separately analyzed segments fulfilling criteria for definite conduction block but also found no association.

In both MMN and MS the primary cause of multifocal inflammation is unknown, but in both diseases auto-immune damage to myelin or nerve antigens are supposed to play a central role in the pathogenesis. MS is considered to be a demyelinating disease, but axonal degeneration has been observed in a recent post-mortem study.[217] In contrast to MS, in MMN the extent of demyelination and axonal damage during the course of the disease can be estimated by electrophysiological examination. In addition, in MMN the clinical assessment of the effects of treatment may be more accurate than in MS as the only neurological manifestation is weakness and the course of the disease in most patients is slowly or stepwise progressive. As both the mechanism of action of IFN-β1a and the effects of IFN-β1a treatment in the individual MS patient are largely unknown, studies on the effect of IFN-β1a treatment in MMN may also have implications for future treatment strategies in MS.

In this prospective study, IFN-β1a was well tolerated despite the known relatively minor, temporary adverse effects. One patient suffered from lung embolism which was unlikely to be related to IFN-β1a therapy. Apart from the temporary deterioration due to the discontinuation of IVIg maintenance therapy at the start of the study in four patients, no further deterioration occurred during the administration of IFN-β1a. The electrophysiological results are in agreement with this as, generally, these showed some improvement rather than deterioration. Our results suggest that IFN-β1a can be prescribed safely in patients with MMN. IFN-β1a and IVIg are both immunomodulatory therapies that are well tolerated and appear to have less serious adverse effects than treatment with immunosuppressants or corticosteroids. Nevertheless the immunomodulatory effects of IFN-β1a seem to differ from IVIg. The onset of improvement in MMN after IVIg infusions is within one or two weeks compared with the six or seven weeks after IFN-β1a in our study. In addition, deterioration usually occurs within weeks of the discontinuation of IVIg, whereas the effect of IFN-β1a seems to sustain itself for several months after discontinuation. This may offer the possibility of treating patients with IFN-β1a for a given period and then discontinuing treatment, whereas with IVIg, long-term maintenance treatment is necessary for most patients.[225] Another advantage is that subcutaneous injection of IFN-β1a can be easily performed by the patient or caregiver at home, while for IVIg infusions, frequent hospital admissions are necessary. A controlled study is necessary to investigate the effect of IFN-β1a treatment in patients with MMN, including newly diagnosed patients with relatively short disease duration.

General discussion

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).

The distribution of muscle weakness at disease onset may help to differentiate between adult-onset lower motor neuron syndromes (table 1). Electrophysiological and laboratory examination may help to differentiate multifocal motor neuropathy (MMN) from lower motor neuron disease (LMND) in the spectrum of lower motor neuron syndromes. As treatment responses may differ it is equally important to differentiate MMN from other immune-mediated neuropathies, e.g. chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal inflammatory demyelinating neuropathy (MIDN). From a clinical viewpoint, all lower motor neuron syndromes may be considered as belonging to one spectrum, with slowly progressive spinal muscular atrophy, showing overlap with ALS, on one side and MIDN, showing overlap with CIDP on the other side (table 1).

In *chapter 3* we described four LMND forms: slowly progressive spinal muscular atrophy, distal spinal muscular atrophy, segmental distal spinal muscular atrophy and segmental proximal spinal muscular atrophy. These lower motor neuron syndromes have been previously described under various names. We propose to describe these LMND forms according to the pattern of weakness. This strategy has the advantage that closely related clinical phenotypes can be more easily identified. For example, to date segmental distal spinal muscular atrophy and segmental proximal spinal muscular atrophy have been considered two separate disease entities as their phenotypes differ. The segmental spreading of symptoms and signs that we observed in both disease forms may point to a common denominator in the largely unknown pathogenesis.

We included 89 patients in our prospective study of LMND. Thirty-seven patients had a disease duration of less than four years, and 35 patients had a disease duration of more than four years. In 17 patients another diagnosis was made (see below). By using a disease duration of over four years as inclusion criterion we attempted to exclude patients with rapidly progressive spinal muscular atrophy or patients with ALS and a lower motor neuron onset in this part of the prospective study (*chapter 4*). We clearly demonstrated disease progression in LMND as muscle weakness and functional impairment significantly increased during follow-up. Deterioration was most marked in patients with slowly progressive spinal muscular atrophy. This impressive increase of weakness and functional impairment and the development of respiratory insufficiency in some of the patients during follow-up, suggest that slowly progressive spinal muscular atrophy must be considered a severe disease form that overlaps with both rapidly progressive spinal muscular atrophy and ALS. Patients

Table 1. Classification of sporadic lower motor neuron syndromes

Disease entity	*Disease course*	*UMN signs*	*Localization of weakness at onset*			*Sensory signs*	*CB / demyel. features*	*anti- GM1 antibodies (%)*	*Treatment options*
			Arms/legs	*Distal/proximal*	*Asymm./symm.*				
ALS	rapidly progr.	yes	arms = legs	distal > proximal	asymm.	no	no	no	riluzole
rapidly PSMA	rapidly progr.	no*	arms > legs	distal > proximal	asymm.	no	no	no	riluzole
slowly PSMA	progr.	no*	legs > arms	distal > proximal	asymm.	no	no	yes (8%)	riluzole
segmental distal SMA	slowly progr.	no	arms	distal	asymm.	no	no	no	no
segmental proximal SMA	slowly progr.	no	arms	proximal	asymm.	no	no	no	no
lower limb amyotrophy	slowly progr.	no	legs	distal > proximal	asymm.	no	no	no	no
distal SMA	slowly progr.	no	legs > arms	distal	symm.	no	no	yes (13%)	no
MMN	slowly progr.	no	arms >> legs	distal >> proximal	asymm.	minor	CB > demyel. features	yes (30%)	IVIg/IFN-β1a
MIDN	slowly progr.	no	arms >> legs	distal >> proximal	asymm.	yes	demyel. features > CB	no	IVIg/prednisone
CIDP	variable**	no	legs > arms	distal > proximal	symm.	yes	demyel. features > CB	no	IVIg/prednisone

*ALS = amyotrophic lateral sclerosis. PSMA = progressive spinal muscular atrophy. SMA = spinal muscular atrophy. MMN = multifocal motor neuropathy. MIDN = multifocal inflammatory demyelinating neuropathy. CIDP = chronic inflammatory demyelinating polyneuropathy. Progr. = progressive. * = UMN signs may develop during the disease course. ** = monophasic or rapidly or slowly progressive or relapsing remitting. Asymm. = asymmetrical. Symm. = symmetrical. CB = conduction block. Demyel. = demyelinating. IVIg = intravenous immunoglobuline. IFN-β1a = interferon-β1a.*

and their relatives should be informed carefully about a possible reduced life expectancy and respiratory function must be monitored in a similar way compared with ALS. The significant decline in muscle weakness and functional impairment in segmental distal spinal muscular atrophy and segmental proximal spinal muscular atrophy could suggest that these segmental LMND forms also should be considered in relation to the ALS-PSMA complex. An alternative explanation could be that these patients suffer from a relatively benign and localized LMND form with an unknown pathogenesis in which superimposed local factors could play a role. In patients with segmental distal spinal muscular atrophy and ongoing progression, Hirayama found evidence of dynamic compression of the lower cervical spinal cord on neck flexion.[88] This could suggest a role for mechanical forces and/or chronic circulatory insufficiency leading to lower cervical anterior horn damage in these patients. In this respect, it would be interesting to study if for example degenerative changes in the lower cervical spine could make patients with segmental LMND forms more at risk for disease progression.

Until now, the glutamate-inhibitor riluzole is the only drug with a significant, though small, therapeutic effect in ALS.[122] As the majority of LMND forms is rare and disease progression is slow, a double blind placebo-controlled study of the effect of riluzole in LMND will be difficult to realize. We presently determine prognostic factors in the 37 patients with a disease duration smaller than four years that were included in our study of LMND. These prognostic factors will hopefully be helpful in identifying patients with more rapidly progressive forms of progressive spinal muscular atrophy, who are eligible for treatment with riluzole and may be included in future trials of new treatment forms in ALS. At present, a well-balanced decision about treating individual patients with LMND with riluzole or not, is only based on the description of the disease course in an individual patient. Given our findings of deterioration in patients with slowly progressive spinal muscular atrophy during a follow-up period of 1 1/2 years, we suggest that these patients could benefit from treatment with riluzole. Whether the other LMND forms should also be treated is less clear.

In 17 of the 89 patients (19%) initially included in our prospective study the diagnosis of LMND proved to be incorrect (*chapter 6*). All 89 patients underwent an extensive standardized electrophysiological examination. In nine patients (10%) conduction block and/or other demyelinating features were found, leading to a diagnosis of MMN in seven patients and CIDP in two patients. These nine patients with immune-mediated neuropathies constituted 82% of all patients with treatable mimic syndromes. The percentage of treatable mimic syndromes in our study is higher than in previous studies of mimics of ALS, most likely because in our study patients with UMN signs had already been excluded. This finding further stresses

the need of a careful analysis of motor nerve conduction in patients with lower motor neuron syndromes.

It remains controversial whether the detection of conduction block or other features of demyelination is obligatory for the diagnosis of MMN. Provided that the electrophysiological examination has been standardized and extensive, the electrophysiological findings play an important role in the set of diagnostic criteria that we proposed for MMN. The finding of definite or probable conduction block was highly predictive of a beneficial response to IVIg (*chapter 7*). However, we have also demonstrated that clinical and laboratory features may contribute to a diagnosis of MMN. In clinical practice, therefore the combination of clinical, laboratory and electrophysiological features should be used in predicting the response to IVIg in patients with lower motor neuron syndromes.

We reported several patients with an asymmetric sensory or sensorimotor demyelinating neuropathy not fulfilling the diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) or MMN, and proposed to call this neuropathy multifocal inflammatory demyelinating neuropathy (MIDN) (*chapter 8*). MIDN is suggested by the finding of asymmetrical weakness and/or sensory symptoms that remain localized in one arm for several years, neuropathic pain, focal nerve tenderness or even a palpable supraclavicular or popliteal mass. We and others have considered MIDN a variant of CIDP. In these patients an extensive electrophysiological examination should be performed. This was initially not done in some of our patients with MIDN and in patients who have been described by others. In up to 20% of these patients other non-immunological diseases were initially considered, resulting in a long diagnostic delay and late treatment. It is important to differentiate MIDN from MMN as most patients with MIDN may benefit from treatment with corticosteroids, whereas patients with MMN do not, or may even deteriorate.[50]

In our patients with MMN, we found a preferential localization of demyelinating features in the nerves of the arms, whereas axonal loss was demonstrated more frequently in longer nerves, occurring most often in the nerves of the legs (*chapter 9*). The preferential localization of demyelination in the nerves of the arms may explain the larger improvement of muscle strength in MMN in the arms than in the legs after IVIg treatment. The different findings in nerves of the arm and of the leg prompt the suggestion that nerves of the arms are more vulnerable for demyelination, and nerves of the legs more vulnerable to axonal loss. The results of our long-term IVIg maintenance treatment study further support different disease mechanisms in nerves of arms and legs as remyelination or reinnervation were predominantly observed in nerves with conduction block, whereas the disease mechanism axonal loss was more often observed in nerves without conduction block, which were significantly more frequent nerves of the legs (*chapter 11*). These observations also favor

a more primary role for axonal degeneration in the pathophysiology of MMN than was previously presumed. These findings must be confirmed in future prospective studies, which combine nerve conduction studies and concentric needle EMG analysis, and could give further insight in the relation between the mechanisms of demyelination and axonal loss during the disease course of MMN.

Previous studies have shown that axons form a major target in demyelinating diseases of the central and peripheral nervous system.[217] In acute motor axonal neuropathy (AMAN), a motor axonal variant of the Guillain-Barré syndrome, frequently high titres of IgG anti-GM1 antibodies are found.[73] The conduction abnormalities in MMN suggest dysfunction at the nodes of Ranvier, where GM1 ganglioside is localized in abundance. The sparse pathological studies in MMN have demonstrated IgM deposits and complement activation at the nodes of Ranvier.[106,191,214] Moreover, binding experiments have shown that binding sites for Gal(β1-3)GalNac moieties of GM1 are present at the paranodal part of the myelin sheath and at axonal membranes.[201] Thus, anti-GM1 antibodies could trigger an inflammatory process which damages both myelin and axons. It is also possible that IgM anti-GM1 antibodies, or other at present unidentified antibodies, could hamper Schwann cell processes in recognizing axonal membrane components and thus interfere with remyelination, leading to persistent conduction block and a primary progressive disease course with little signs of remission. Another indication for an ongoing immunological process is the finding of a persistent impairment of the blood-nerve barrier in MMN.[104] In addition, IgM antibodies could through complement activation also cause ion channel dysfunction at the nodes of Ranvier.[166,201] Differences in ion channel distributions between for example nerves of the arms and of the legs might explain a greater susceptibility to conduction block of arm nerves in demyelinating diseases (*chapter 9*).

We observed a response rate of 90% to IVIg treatment in our patients with MMN (*chapter 10*). Even in MMN patients with a long disease duration and severe demyelination and axonal degeneration, the slowly progressive muscle weakness and disability appeared to result from an ongoing immune-mediated process. This notion justifies installment of treatment in patients during all stages of the disease. IVIg maintenance treatment has therefore become the standard treatment of MMN. We have not only shown that this treatment had a beneficial effect on muscle strength and disability over a period of 4 - 8 years, but also found that IVIg treatment favorably influenced mechanisms of remyelination (*chapter 11*). Thus, long-term IVIg maintenance treatment seems rational in MMN. However, the high cost of IVIg and the frequent, burdensome infusions, have prompted the search for adjuvant immunosuppressive therapies. Cyclophosphamide may induce a favorable response, but toxicity limits its use in patients with MMN, who are usually young. Therefore,

new controlled studies with IVIg and as adjuvant less toxic immunosuppressants, like azathioprine or mycophenolate mofetil[27], are needed.

Our open pilot-study with interferon-β1a (22 μg, 3 x subcutaneously /week) in MMN showed a favorable, long lasting, response in three mildly affected patients with a relatively short disease duration (*chapter 12*). We have additionally treated nine MMN patients with interferon-β1a, four of whom responded favorably. These four responders and one of the three responders of the pilot-study, are at present being treated during another six months with 44 μg interferon-IFN-β1a (3x/w). Three of five patients in this study responded. One showed a better response on 44 μg than on 22 μg interferon-IFN-β1a. In two others no conclusions can yet be drawn. Since interferon-β1a monotherapy is less expensive than IVIg and continuous treatment may not be necessary, it could prove an attractive alternative to IVIg. After discontinuation of interferon-β1a seven responders showed sustained improvement for a mean period of 10 months. Of course, this positive effect of interferon-β1a must be confirmed in a future controlled trial. Because the IVIg maintenance dosage in our non-responders was lower during than before treatment with interferon-β1a, it will also be interesting to study the use of interferon-β1a as adjuvant treatment. A positive effect of interferon-β1a as adjuvant treatment in CIDP has been described by others.[118]

The pathogenesis of sporadic LMND and of MMN is still largely unknown. A majority of affected patients with these lower motor neuron syndromes is male, suggesting that not yet identified genetic, hormonal, or other occupational or life-style factors could play a role in the pathogenesis. By increasing the risk of developing disease DNA mutations, for instance in the SMN2 gene, could act as susceptibility factors in progressive spinal muscular atrophy and ALS (*chapter 2*), but also in other sporadic LMND forms. Until these possible underlying pathophysiological mechanisms have been identified, 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 electrophysiological and laboratory 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 LMND forms or with IVIg or IFN-β1a in MMN and MIDN.

In conclusion, the spectrum of lower motor neuron syndromes is wide and ranges from progressive spinal muscular atrophy, which shows overlap with ALS, to MIDN, which shows overlap with CIDP. 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.

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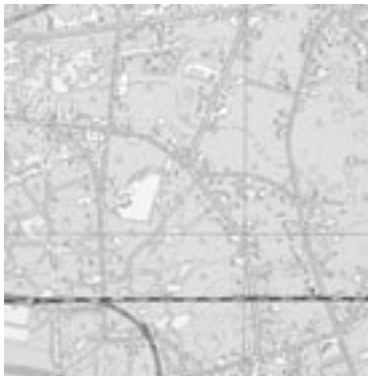

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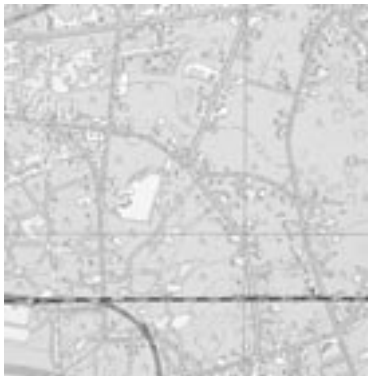
Summary



This thesis focusses 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 progressive spinal muscular atrophy, but were also significant for patients with segmental 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 hereditary form of LMND with adult onset and rapid progression. No involvement of upper motor neurons was found either clinically or pathologically. Disease progression 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 presentation 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 diagnoses include: MMN (7), chronic inflammatory demyelinating polyneuropathy (CIDP) (2), inflammatory myopathy (1), myasthenia gravis (1). The remaining six patients were diagnosed as having myopathy, syringomyelia, slowly progressive ALS, chronic idiopathic axonal polyneuropathy, 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 T_2 -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.

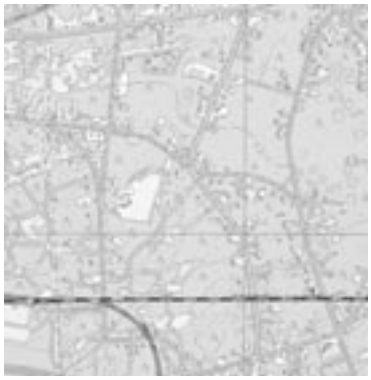
As the effect of IVIg treatment in MMN lasts only several weeks, IVIg maintenance treatment is often necessary to maintain the effect on muscle strength. As IVIg maintenance treatment is expensive, and the frequent infusions may be burdensome to patients, it is important to know whether IVIg maintenance 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.

Samenvatting



Samenvatting

Zenuwcellen die door hun uitlopers de spieren aansturen (motorische neuronen) zijn zowel in de hersenen gelokaliseerd (centraal gelegen motorische neuronen) als in de hersenstam en het ruggenmerg (perifeer gelegen motorische neuronen). Bij ziekten van motorische neuronen kunnen de centraal en perifeer gelegen motorische neuronen afzonderlijk of beiden aangedaan zijn. De ziekte waarbij zowel centraal als perifeer gelegen motorische neuronen zijn aangedaan, heet amyotrofische lateraalsclerose (vanaf nu afgekort als ALS). ALS is een ernstige ziekte, waarbij de meerderheid van de patiënten binnen een paar jaar aan zwakte van de ademhalingsspieren komt te overlijden. Het onderzoek in dit proefschrift beschreven richt zich op die groep aandoeningen waarbij alleen de perifeer gelegen motorische neuronen zijn aangedaan ('lower motor neuron syndromes') en de spieren van de ledematen dunner (atrofisch) worden en verzwakt raken. Het betreft een relatief zeldzame en slecht omschreven groep aandoeningen.

Binnen de groep van aandoeningen van perifeer gelegen motorische neuronen is het belangrijk om een onderscheid te maken of primair de zenuwcel zelf of de zenuwuitloper (axon) al of niet met de omringende witte stof (myeline) is aangedaan. In het eerste geval spreken we van ziekten van de perifeer gelegen motorische neuronen ('lower motor neuron disease', LMND), en in het tweede geval van motorische neuropathieën. Van deze laatste groep zijn chronische inflammatoire demyeliniserende polyneuropathie (CIDP), waarbij naast krachtsverlies ook stoornissen van het gevoel (sensibiliteit) voorkomen, en multifocale motorische neuropathie (MMN) de belangrijkste. Zowel van CIDP als van MMN wordt gedacht dat de ziekte wordt veroorzaakt door een stoornis in het afweersysteem (immuunsysteem). Waarschijnlijk raakt de zenuw op meerdere plaatsen ontstoken en treedt er verlies van myeline op (demyelinisatie), waardoor zenuwgeleiding minder goed mogelijk is. Dit leidt soms tot geleidingsblokkade, met spierzwakte als gevolg. Als het axon betrokken raakt in het ziekteproces, kan deze verloren gaan waardoor er ook spierzwakte ontstaat. Door onderzoek van de zenuwgeleiding (neurofysiologisch onderzoek) kan geleidingsblokkade aangetoond worden. Auto-immuunziekten als MMN zijn in het algemeen behandelbaar met medicijnen die aangrijpen op het immuunsysteem. Daarom is het belangrijk om onderscheid te maken tussen LMND en MMN. Hierin speelt het neurofysiologisch onderzoek een belangrijke rol.

In het afgelopen decennium hebben zich veel ontwikkelingen voorgedaan binnen het neurofysiologisch onderzoek naar neuropathieën en binnen de diagnostiek naar erfelijke aandoeningen. Daardoor zijn eerdere studies naar aandoeningen van perifeer gelegen motorische neuronen verouderd geraakt en is een nieuwe classificatie

noodzakelijk. Bovendien is weinig bekend over het beloop en de behandeling van de verschillende aandoeningen van perifeer gelegen motorische neuronen. *Hoofdstuk 1* geeft een algemene inleiding over "lower motor neuron syndromes" en beschrijft het doel van het onderzoek dat in dit proefschrift is beschreven. Ten eerste hebben we geprobeerd de classificatie van de aandoeningen van perifeer gelegen motorische neuronen te verbeteren. Ten tweede is het natuurlijk beloop van verschillende aandoeningen van perifeer gelegen motorische neuronen in kaart gebracht. Ten derde hebben we in het kader van de behandeling de veronderstelde onderliggende ziektemechanismen van MMN beschreven.

Hoofdstuk 2 geeft een overzicht van de bestaande literatuur over aandoeningen van perifeer gelegen motorische neuronen. In *hoofdstuk 3* beschrijven we de klinische en neurofysiologische kenmerken van 49 patiënten met LMND, waarbij door middel van genetisch onderzoek bekende erfelijke vormen van LMND uitgesloten zijn (het gaat dus om zogenoemde sporadische vormen). Bovendien hadden alle patiënten langer dan vier jaar verschijnselen van de ziekte, zodat ALS als mogelijke diagnose minder waarschijnlijk was. Wij vonden dat er op basis van de verdeling van de spierzwakte vier vormen van LMND te onderscheiden zijn:

(1) Langzaam progressieve spinale spieratrofie: 13 patiënten hadden wijdverspreide spierzwakte in armen en benen.
(2) Distale spinale spieratrofie: 8 patiënten hadden symmetrische zwakte van de spieren van onderarmen en onderbenen (distaal).
(3a) Segmentale distale spinale spieratrofie : 14 patiënten hadden distale spierzwakte in één arm (asymmetrisch).
(3b) Segmentale proximale spinale spieratrofie: 14 patiënten hadden asymmetrische zwakte in de rond de schouder gelegen spieren (proximaal). In de groepen 3a en 3b bleek dat de ziekte zich in het ruggenmerg uitgebreid had tot nabij gelegen groepen zenuwcellen, hetgeen de term segmentaal verklaart.

Vergeleken met de andere groepen was de gemiddelde leeftijd in groep 1 hoger, was de spierzwakte ernstiger en waren de functionele beperkingen in het dagelijks leven groter. Alleen in groep 1 werd bij een aantal patiënten een verminderde ademhalingsfunctie gevonden. In alle groepen waren de afwijkingen gevonden bij het neurofysiologisch onderzoek wijder verspreid dan de spierzwakte. De voorgestelde classificatie beoogt het onderscheid tussen de verschillende vormen van LMND in de toekomst gemakkelijker te maken.

Om het natuurlijk beloop van LMND te onderzoeken, vervolgden we 35 van bovengenoemde patiënten gedurende 1,5 jaar. Van deze zogenoemde prospectieve studie beschrijven we in *hoofdstuk 4* de resultaten. Bij alle patiënten nam de spierkracht duidelijk af en namen de functionele beperkingen en het aantal regio's van de ledematen met zwakte toe. De klinische achteruitgang bleek het grootst te zijn in

groep 1, maar was ook duidelijk aanwezig in de groepen 3a en 3b. In groep 1 ontwikkelde de helft van de patiënten ademhalingsproblemen, waaraan uiteindelijk 2 patiënten overleden. Eén van deze twee patiënten ontwikkelde ook afwijkingen in de centraal gelegen motorische neuronen, zodat de diagnose gewijzigd werd in ALS. De verschillende vormen van LMND toonden dus een duidelijk progressief beloop. Met name langzaam progressieve spinale spieratrofie is een ernstig ziektebeeld, dat overlap vertoont met ALS. Het valt daarom te overwegen patiënten met langzaam progressieve spinale spieratrofie te behandelen met riluzole, het enige medicijn waarvan tot nu toe is bewezen dat het de voortschrijding van ALS vertraagt.

In *hoofdstuk 5* beschrijven we twee families met elk drie familieleden met een erfelijke vorm van LMND met een autosomaal dominante overervingswijze. In beide families verliep de ziekte snel progressief en overleden de patiënten binnen enkele jaren aan zwakte van de ademhalingsspieren. Dit verschilt van wat in de literatuur beschreven is over autsomaal dominante vormen van LMND, die vaak relatief mild zouden verlopen. In familie A was er sprake van symmetrische spierzwakte in de ledematen en in familie B was de spierzwakte asymmetrisch. Op het stoffelijk overschot van één patiënt uit elke familie werd sectie (pathologisch onderzoek) verricht. In familie A toonde het pathologische onderzoek verschijnselen aan die beschreven zijn bij niet-dominant (autosomaal recessief) overervende vormen van spinale spieratrofie, die vaak op de kinderleeftijd de eerste verschijnselen geven. In familie B werden pathologische verschijnselen gevonden die bij ALS beschreven zijn. Omdat onderzoek naar de in 1999 bekende genafwijkingen bij ALS geen afwijkingen opleverde, gaat het in de laatste familie waarschijnlijk om een nog onbekende vorm van erfelijke ALS, met alleen klinische verschijnselen van perifeer gelegen motorische neuronen. De ziektebeelden in de beide families verbreden ons inziens het spectrum van de verschillende vormen van LMND.

Bij 17 van de 89 patiënten die voor het onderzoek naar het natuurlijk beloop van LMND uitgebreid werden onderzocht, werd een andere diagnose gesteld: de zogenaamde 'mimic syndromes' (*hoofdstuk 6*). In 11 gevallen betrof het een behandelbare aandoening. Bij 9 patiënten werden bij uitgebreid neurofysiologisch onderzoek verschijnselen gevonden die passen bij demyelinisatie en kon zo de diagnose worden gewijzigd in MMN bij 7 patiënten en in CIDP bij 2 patiënten. Dit onderstreept het belang van dit type onderzoek bij patiënten met een mogelijke diagnose LMND.

De ziekte MMN werd pas voor het eerst beschreven in 1988, en diagnostische criteria zijn in de internationale literatuur niet beschreven. In *hoofdstuk 7* beschrijven we diagnostische criteria voor MMN die we hebben opgesteld nadat we 37 patiënten met aandoeningen van perifeer gelegen motorische neuronen hadden onderzocht. Dit onderzoek bestond uit: meting van de spierkracht, bloedonderzoek naar het

spierenzym creatine kinase (CK), antistoffen tegen een bestanddeel van het myeline (GM1), onderzoek van het hersenvocht (liquor) en beeldvorming door middel van een magneetscan (MRI) van het bij de schouders gelegen zenuwvlechtwerk (plexus brachialis). Ook vond uitgebreid neurofysiologisch onderzoek plaats, waarbij verschijnselen die passen bij demyelinisatie als volgt werden geclassificeerd: definitieve geleidingsblokkade, waarschijnlijke geleidingsblokkade, of vertraging van de zenuwgeleiding zonder dat geleidingsblokkade aangetoond kon worden. Tenslotte werden bij het opstellen van de criteria de reactie op een behandeling met gezuiverde afweerstoffen van bloeddonoren die via een infuus toegediend worden (intraveneuze immuunglobulines, IVIg) meegenomen en werd een extra klinisch onderzoek na één jaar gebruikt. Aan de hand van de opgestelde criteria konden de volgende diagnoses worden gesteld:

(1) definitieve MMN: 21 van de 37 patiënten voldeden hieraan, waarvan 17 (81%) gunstig reageerden op IVIg behandeling,
(2) waarschijnlijke MMN: 7 patiënten voldeden hieraan, waarvan 5 gunstig reageerden op IVIg-behandeling (71%), en
(3) mogelijke MMN: 9 patiënten, waarvan er één gunstig reageerde (11%).

In categorie 3 is de kans op de diagnose LMND groter dan in de categorieën (1) en (2). Belangrijke voorspellers voor de diagnose MMN in plaats van LMND, en daarmee een grotere kans op een gunstige reaktie op IVIg-behandeling, waren: een lage beginleeftijd, gelokaliseerde spierzwakte en een niet-verhoogd CK. Wij stellen voor deze diagnostische criteria voor MMN in de klinische praktijk toe te passen en de toepasbaarheid ervan te evalueren.

Er is een groep patiënten die niet voldoet aan de diagnostische criteria voor de ziekte CIDP, zoals die beschreven zijn in de literatuur, noch aan de boven beschreven criteria voor MMN. In *hoofdstuk 8* presenteren we de klinische, neurofysiologische, radiologische en pathologische karakteristieken van zes van deze patiënten. Bij alle patiënten was er sprake van een asymmetrisch patroon van spierzwakte en gevoelsstoornissen. Bij neurofysiologisch onderzoek werden bij alle patiënten verschijnselen die passen bij demyelinisatie gevonden in zowel motorische als sensibele zenuwen. Op een MRI-scan van de plexus brachialis werd bij vier patiënten, na toediening van intraveneus contrast, een verdikking en versterkte aankleuring gezien, hetgeen ook bij andere auto-immuunziekten is beschreven. Een chirurgisch verwijderd stukje weefsel (biopt) uit de plexus brachialis van één patiënt liet bij pathologisch onderzoek tekenen van ontsteking zien. Alle zes patiënten reageerden gunstig op behandeling met IVIg. Wij stellen voor deze aandoening multifocale inflammatoire demyeliniserende neuropathie (MIDN) te noemen. Verder beschrijven we 34 patiënten uit de internationale literatuur met een vergelijkbaar klinisch beeld. Omdat MIDN behandelbaar is, en er zowel bij onze zes als bij de andere 34 patiënten in

eerste instantie vaak aan een niet-behandelbare ziekte werd gedacht, is het belangrijk om MIDN als een aparte klinische entiteit te beschouwen, met kenmerken van zowel CIDP als MMN.

In *hoofdstuk 9* beschrijven we de resultaten van een onderzoek naar de verdeling van afwijkingen die bij neurofysiologisch onderzoek in 39 patiënten met MMN werden gevonden. Zowel geleidingsblokkade als verlies van axonen in een bepaalde zenuw bleken positief te zijn gecorreleerd met zwakte in spieren die door de betreffende zenuw werden aangestuurd. Ook bleken de verschijnselen die passen bij demyelinisatie willekeurig verdeeld over de verschillende segmenten van de zenuw, en dus vaker in langere zenuwen, voor te komen. Verlies van axonen werd vaker waargenomen in langere dan in kortere zenuwen. Omdat de zenuwen naar distaal gelegen spieren langer zijn, verklaren deze bevindingen het feit dat in MMN distale spieren meer zijn aangedaan dan proximale spieren. Voor de bevinding dat verschijnselen die passen bij demyelinisatie vooral in armzenuwen gevonden werden, terwijl in de langere beenzenuwen vooral verlies van axonen werd aangetoond, hebben wij vooralsnog geen duidelijke verklaring. Mogelijk liggen aan de afwijkingen in de beenzenuwen andere ziektemechanismen ten grondslag dan aan die in de armzenuwen. In de praktijk kunnen deze resultaten worden toegepast: bij het voor de patiënt belastende neurofysiologische onderzoek verdient het de voorkeur eerst armzenuwen die verzwakte spieren aansturen te onderzoeken op de aanwezigheid van geleidingsblokkade, en andere verschijnselen die passen bij demyelinisatie. Hierna moeten armzenuwen die niet-verzwakte spieren aansturen worden onderzocht. Er moet pas over worden gegaan tot onderzoek in de beenzenuwen als in alle armzenuwen geen afwijkingen zijn gevonden.

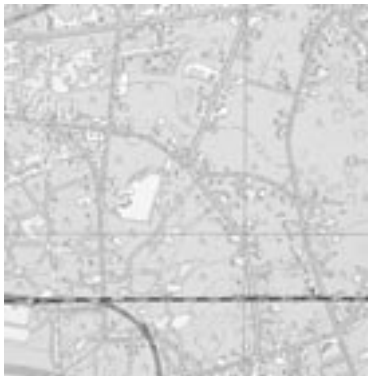
Omdat de meerderheid van de patiënten met MMN gunstig blijkt te reageren op IVIg-behandeling, is dit momenteel de standaardbehandeling voor patiënten met MMN. Een prospectieve studie naar het natuurlijke beloop van de ziekte is daarom ethisch niet meer verantwoord. Wij voerden daarom een retrospectieve studie uit: 38 patiënten met MMN werden eenmalig onderzocht en de ernst van de gevonden klinische en neurofysiologische afwijkingen werd gerelateerd aan de ziekteduur, die varieerde van 6 maanden tot 34 jaar (*hoofdstuk 10*). Bij patiënten met een langere ziekteduur werden duidelijk meer afwijkingen gevonden, hetgeen aantoont dat MMN een langzaam progressieve ziekte is. Tevens onderzochten we in alle patiënten de reaktie op IVIg-behandeling. We vonden dat ook patiënten die al relatief lang ziek zijn en ernstige spierzwakte hebben, gunstig reageerden. Dit laatste heeft consequenties voor de klinische praktijk. Ook bij patiënten bij wie de diagnose laat is gesteld, is behandeling zinvol.

Het effect van een standaardkuur IVIg (dagelijks 0,4 g/kg lichaamsgewicht gedurende 5 dagen) in MMN houdt meestal slechts enkele weken aan. De meeste patiënten

hebben dan ook onderhoudsbehandeling nodig om in het dagelijks leven goed te kunnen blijven functioneren. De behandeling met IVIg is echter belastend voor de patiënt en zeer kostbaar. In *hoofdstuk 11* beschrijven wij de resultaten van een onderzoek naar het lange termijneffect van IVIg bij 11 patiënten met MMN, die 4 - 8 jaar behandeld werden. De spierkracht werd onderzocht en neurofysiologisch onderzoek werd uitgevoerd voor en na de eerste standaardkuur en daarna jaarlijks. Na de eerste standaardkuur IVIg verbeterde de spierkracht en namen de functionele beperkingen in het dagelijkse leven duidelijk af. Tijdens het vervolg van de behandeling bleef de spierkracht beter dan voor start van de IVIg, niettemin was er een geleidelijke en duidelijke achteruitgang. Bij het neurofysiologisch onderzoek werd verbetering van de zenuwgeleiding met name in die zenuwen gevonden waar eerder verschijnselen die passen bij demyelinisatie waren gevonden. Verslechtering van de zenuwgeleiding of zelfs verlies van axonen werd voornamelijk gezien in zenuwen zonder verschijnselen die passen bij demyelinisatie. Hieruit is te concluderen dat de lange termijn-behandeling met IVIg in MMN een gunstig effect heeft op spierkracht en verschijnselen die passen bij demyelinisatie, maar dat een lichte achteruitgang in spierkracht en verlies van axonen niet kan worden voorkomen.
Doordat aan IVIg-behandeling bovengenoemde nadelen kleven, is het belangrijk om naar nieuwe behandelingen voor MMN te zoeken. In *hoofdstuk 12* beschrijven wij de resultaten van een studie naar het effect van interferon-β1a (IFN-β1a) bij negen patiënten met MMN. IFN-β1a is geregistreerd voor de behandeling van multiple sclerose, een demyeliniserende auto-immuunziekte van het centrale zenuwstelsel. De opzet van de studie was open, d.w.z dat zowel de behandelend arts als de patiënt wist welk medicijn de patiënt kreeg en welke dosering. De patiënten werden gedurende zes maanden drie keer per week met IFN-β1a behandeld. De onderhoudsbehandeling met IVIg die vijf patiënten voor de start van de studie kregen, werd gestopt. De spierkracht verbeterde en de functionele beperkingen in het dagelijkse leven namen af bij drie patiënten. Deze verbetering was groter dan na IVIg-behandeling en hield nog maanden na het stoppen van de IFN-β1a injecties aan. De drie patiënten die verbeterden waren relatief kort ziek en nog niet ernstig aangedaan. De bijwerkingen van IFN-β1a waren mild en voorbijgaand. Duidelijke achteruitgang in de zenuwgeleiding tijdens behandeling met IFN-β1a werd niet gevonden. Vier van de zes patiënten die niet verbeterden, gingen zodanig achteruit dat de onderhoudsbehandeling met IVIg weer herstart moest worden. Wij hebben geconcludeerd dat het effect van IFN-β1a in MMN gematigd positief lijkt en dat een geblindeerde studie, waarbij zowel de behandelend arts als de patiënt niet weet of de patiënt IFN-β1a of een schijngeneesmiddel (placebo) krijgt, aan te bevelen is.
De resultaten van dit proefschrift worden bediscussieerd in *hoofdstuk 13*. De oorzaak van de ziekte LMND is in de meeste niet-erfelijke vormen onbekend. Ook over de

precieze ziektemechanismen in MMN is niet veel bekend. Daarom is het het meest praktisch om de verschillende aandoeningen van perifeer gelegen motorische neuronen in te delen op basis van die gegevens die wel bekend zijn, zoals het patroon van de spierzwakte en de bevindingen bij laboratorium-, neurofysiologisch, radiologisch en eventueel pathologisch onderzoek. Dit proefschrift laat zien dat de door ons beschreven aandoeningen van perifeer gelegen motorische neuronen als een spectrum van aandoeningen is te beschouwen, met aan de ene kant de ziekte langzaam progressieve spinale spieratrofie, die overlap vertoont met ALS en aan de andere kant MIDN, die overlap vertoont met CIDP. Voor de individuele patiënt is het zeer belangrijk om onderscheid te kunnen maken tussen de verschillende vormen. De behandelend arts kan zo adequate informatie geven over het te verwachten beloop van de ziekte en kan de patiënten met langzaam progressieve spinale spieratrofie behandelen met riluzole en patiënten met MMN of MIDN behandelen met IVIg of IFN-β1a.

Dankwoord



Allereerst gaat mijn dank uit naar alle patiënten die mee hebben gewerkt aan de onderzoeken die in dit proefschrift beschreven zijn. Patiënten met aandoeningen van perifeer gelegen motorische neuronen zijn niet alleen zelf zeer gemotiveerd om meer over hun aandoening te weten te komen, maar tonen ook een grote betrokkenheid met (toekomstige) lotgenoten. Dit maakt dat ze, hierin vaak gesteund door hun partner en/of familieleden, open staan voor wetenschappelijk onderzoek en bereidwillig hun medewerking verleenden aan soms langdurige en belastende onderzoeken.

Ik wil daarnaast de medewerkers van de polikliniek neurologie en de afdeling klinische neurofysiologie bedanken, die altijd een onderzoekskamer of een plekje in de waterbakken voor me wilden regelen. Ook Joyce Oerlemans bedank ik voor de secretariële ondersteuning. De collegialiteit van mijn collega arts-assistenten, zeker in de laatste fase, heb ik zeer gewaardeerd. Ik ben weer helemaal klaar voor een borrel op vrijdag...

Dan wil ik de mensen bedanken die niet alleen mij, maar ook de inhoud van dit boekje, hebben "gekneed" tot wat nu voor u ligt:

Prof. Dr. J.H.J. Wokke, beste John, je bent als promotor tijdens de gehele onderzoeksperiode een grote motivator geweest, wiens kracht het was om zeer scherp de grote lijn van het onderzoek in de gaten te houden. Ook heb je me in de onderzoekskamer veel over neuromusculaire ziekten geleerd, eerst als keuze co-assistent en daarna als onderzoeksassistent. Je enthousiasme over geaccepteerde artikelen en een gewonnen prijs -waar ik ook heel blij mee was, al liet ik het misschien niet altijd zo duidelijk merken - en de onvoorwaardelijke steun tijdens voordrachten, hebben me als onderzoeker veel vertrouwen gegeven.

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Dr. L.H. van den Berg, beste Leonard, ik ben jou als co-promotor veel dank verschuldigd voor vele facetten van dit proefschrift, variërend van het schrijven van de

eerste subsidie-aanvraag, het soms eindeloos schaven aan tabellen en -pas als die af waren- aan de tekst van manuscripten, het met Hessel brainstormen over de grote lijn van een volgend artikel, tot het leggen van contacten met mensen buiten onze afdeling neurologie. Dit alles heeft geleid tot een lijst publikaties waar ik aan het begin van dit onderzoek niet van had durven dromen.

Dr. H. Franssen, beste Hessel, ook jou als co-promotor ben ik veel dank verschuldigd. Je hebt me niet alleen veel over klinische neurofysiologie, en in het bijzonder geleidingsblokkade geleerd, maar ook veel bijgedragen aan andere onderdelen van een groot aantal hoofdstukken van dit proefschrift. Ik zal de brainstorm- en rekensessies (met ouderwetse rekenmachine) in de "vissenkom" niet gauw vergeten, en evenmin je commentaar op artikelen, dat altijd keurig met potlood geschreven was. Tussen de wetenschappelijke bezigheden door en op de fiets terug naar Bunnik, heb ik ook andere kanten van je leren kennen: je fascinerende fascinatie voor treinen en alles wat nodig is om ze op tijd te laten rijden -kan de NS niet bij je in de leer?- en je twijfels over of je wel of niet je baard zal laten staan.

Prof. Dr. J. van Gijn, geachte professor, ik wil u bedanken voor het creëren van een klimaat waarin opleiding en onderzoek naadloos op elkaar aansluiten en elkaar positief beïnvloeden. Zo leert de onderzoeker in ons beter met patiënten omgaan en de klinicus in ons om kritisch na te denken over de waarde van diagnostische en therapeutische mogelijkheden voor de patiënt. Over een geheel ander klimaat gesproken: in de winter ga ik graag nog eens de strijd op de schaats met u aan...

Prof. Dr. V.M.B.J. de Jong, beste Vianney, jouw kennis over ALS en je betrokkenheid bij de patiënten met deze ziekte, heeft veel indruk op me gemaakt. Bedankt voor het luisterend oor tijdens de besprekingen, maar ook voor het leggen van contacten met andere ALS-specialisten.

Prof. Dr. R.J. de Haan, beste Rob, veel dank voor je bijdrage aan verscheidene artikelen. Je nuchtere kijk op wat je met neuromusculaire onderzoeksdata wel en, gezien de relatief kleine patiëntenaantallen, soms vooral niet kan doen is voor mij zeer waardevol geweest.

Prof. Dr. P.N. Leigh, dear professor, I acknowledge your comments on chapter 5.
I am honoured that you consented in participating in the Commission and thank you for your presence during the defense of my thesis.

Dr. S. Kalmijn, beste Sandra, jouw komst naar de neuromusculaire onderzoeksgroep

was een verademing nadat ik, samen met de andere neuromusculaire onderzoeksassistenten, jarenlang "rond gezwommen" had met epidemiologische vragen. Je hulp in de laatste fase bij de twee "PSMA-stukken" waardeer ik enorm. In korte tijd torpedeerde ik je met verzoeken, met steeds weer net een andere groepsindeling waardoor jij alle analyses opnieuw kon doen, waar je steeds rustig en aardig onder bleef.

Drs. J. Visser, beste Jeldican, het feit dat we ons met het prospectieve onderzoek over PSMA op vrijwel onontgonnen terrein begaven was soms wel lastig, maar heeft de samenwerking in korte tijd hecht gemaakt. Veel dank voor de uitwisseling van gegevens, waaronder jouw mimic's-stuk dat één van de hoofdstukken uit dit proefschrift is geworden, en de ideeën over hoe die gegevens te interpreteren. Op naar jouw boekje..

Drs J.T.H. van Asseldonk, beste Thies, terwijl ik als klinisch onderzoeker me met voorzichtige stappen op het klinisch neurofysiologische pad waagde, nam jij met de flair van een fysisch beter onderlegde onderzoeker het estafette-stokje over. Hiervan is hoofdstuk 9 het bewijs en ik ben er trots op dat het één van mijn hoofdstukken mocht worden. Jouw klinisch neurofysiologisch onderzoek naar LMND en MMN ziet er veelbelovend uit.

"Kopkamer"genoten Wendy Bosboom, Marijke Eurelings, Geert-Jan Groeneveld, Marjon van der Meulen, Laurien Teunissen, Jan Veldink en Alexander Vrancken,
met elk van jullie heb ik in wisselende combinaties in de ruimte gebivakkeerd waar klimatologisch geen eer meer aan te behalen valt. In deze ruimte is niettemin de basis gelegd voor veel Utrechts neuromusculair wetenschappelijk werk en heb ik vele gezellige uren doorgebracht. Wendy, Marjon en Laurien, bedankt voor jullie leeswerk en betrokkenheid bij ook niet-neurologische zaken.

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en endocrinologisch vlak leverden aan enkele artikelen, of aan artikelen in wording...

Lieve kubieke zussen Mariken en Eveline, Doranda en Anja en Maaike, bedankt voor de onvoorwaardelijke vriendschap waarin ruimte bestaat voor een lach maar ook voor een traan. Dat ik in de afgelopen drukke maanden niet één keer een afspraak met jullie heb laten voorbij gaan, zegt genoeg.

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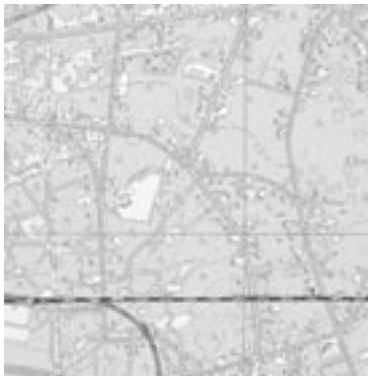
Lieve papa en mama, ik wil jullie bedanken, niet alleen voor de liefde waar jullie Maaike en mij altijd mee hebben omringd, maar ook voor de hartverwarmende liefde die jullie Philippe en Vincent geven. Zonder de enorme hulp en steun en de warme thuisbasis die jullie hebben gecreëerd voor onze jongetjes, hadden we het de afgelopen drukke periode niet gered. Het onvoorwaardelijke vertrouwen in hoe Maaike en ik de dingen aanpakken, vormt mijns inziens de basis voor onze hechte familieband.

Lieve Herman, wat zal ik over jou schrijven, die zo'n grote bijdrage heeft geleverd aan dit proefschrift, in de hoedanigheid van -in oplopende volgorde van belangrijkheid- systeembeheerder, virusjager, database-expert, kok, rots in de branding, echtgenoot en vader? Dat ik van je hou.

Lieve Philippe en Vincent, door jullie komst is veel betrekkelijk geworden, ook promoveren...

Curriculum vitae



Renske van den Berg-Vos werd geboren op 16 juni 1970 te Utrecht. Na in Vleuten en Durham, North Carolina (USA) gewoond te hebben, werd Maarn voor lange tijd haar vaste woonplaats, waar zij de basisschool doorliep. Na het afronden van het VWO op de KSG de Breul in Zeist, ging zij in 1988 geneeskunde studeren en wonen in Utrecht. Tijdens haar studententijd was zij o.a. actief in de almanakraad van de faculteitsvereniging MSFU Sams en was zij als voorzitter betrokken bij de organisatie van een landelijk congres voor studenten geneeskunde. De inmiddels ontstane belangstelling voor de neurowetenschappen leidde er toe dat zij o.a. het student-assistentschap 'anatomie van het menselijk brein' ging geven. Na een keuze co-schap neuromusculaire ziekten bij professor Wokke in 1995 en een korte omzwerving als AGNIO neurologie in Tilburg, begon zij per 1 september 1996 als AGIKO aan haar opleiding tot neuroloog en klinisch onderzoeker (opleider prof.dr. J. van Gijn, onderzoeksbegeleider prof.dr. J.H.J. Wokke), die zij in 2005 hoopt af te ronden. Het onderzoek dat in dit proefschrift beschreven is, voerde zij uit vanaf november 1997. Voor het deel van het onderzoek dat in hoofdstuk 7 beschreven is, kreeg zij de Prinses Beatrix Fonds-jaarprijs neuromusculaire ziekten 2001. Van 1996 tot 2001 was zij bestuurslid van de Vereniging van Arts-Assistenten in opleiding tot Neuroloog (VAAN), en hierbinnen actief o.a. als lid van het Consilium Neurologicum, als bestuurslid van de Landelijke Vereniging van Assistent-Geneeskundigen (LVAG) en als voorzitter. Zij is getrouwd met Herman van den Berg en zij hebben twee zonen: Philippe en Vincent.

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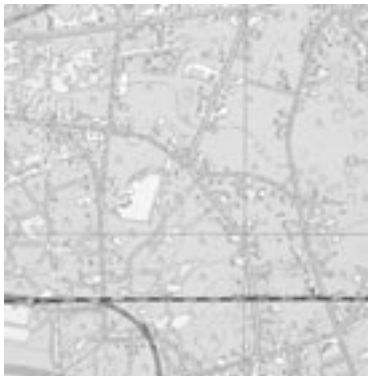

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