Electrodiagnostic studies in Guillain-Barré syndrome

Electrodiagnostic studies in Guillain-Barré syndrome

(Elektrodiagnostisch onderzoek van het Guillain-Barré syndroom)

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aan mijn moeder en mijn vader
aan Atie

Contents

The following chapters of this thesis were adapted from articles, published or submitted for publication:

Chapter 2. The technique and interpretation of motor nerve conduction studies. Submitted.

Chapter 4. Electrodiagnostic findings in the Guillain-Barré syndrome. Submitted.

Chapter 5. Electrodiagnostic criteria for polyneuropathy and for demyelination: application in 135 Guillain-Barré patients. Submitted.

Chapter 6. Prognostic value of electrodiagnostic testing in the Dutch Guillain-Barré trial. Submitted.

Chapter 7. Axonal damage in the Guillain-Barré syndrome. Meche van der FGA, Meulstee J, Kleijweg RP. Muscle Nerve 1991: 14; 997-1002. Reprinted with permission. John Wiley & Sons, Inc. 1991.

List of abbrevations

AIDP	Acute inflammatory demyelinating polyneuropathy
ALS	Amyotrophic lateral sclerosis
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMAP	Compound muscle action potential
CSNAP	Compound sensory nerve action potential
DML	Distal motor latency
DP	Density of denervation potentials
EAN	Experimental allergic neuritis
EMG	Electromyography and nerve conduction studies
F-lat.	F-response latency
GBS	Guillain-Barré syndrome
HMSN	Hereditary motor and sensory neuropathy
IvIg	Intravenous immune globulin
LLN	Lower limit of normal
M. APB	Abductor Pollicis brevis muscle
M. ADV	Abductor Digiti minimi muscle
M. TA	Anterior Tibial muscle
M. EDB	Extensor Digitorum brevis muscle
m-NCV	Motor nerve conduction velocity
MMN	Multifocal motor neuropathy
MUP	Motor unit potential
Pattern	Recruitment pattern on maximal voluntary effort
PE	Plasma exchange
s-NCV	Sensory nerve conduction velocity
ULN	Upper limit of normal

General Introduction

The Guillain-Barré syndrome (GBS) is a monophasic (sub)acute inflammatory demyelinating predominantly motor polyradiculo-neuropathy. Clinical criteria have been proposed by Asbury (Asbury et al., 1978; Asbury and Cornblath, 1990). GBS is a selflimiting disease, however, up to 30% of the patients may need temporary artificial ventilation; about 15% remain disabled and mortality is estimated to be up to 5%. Therefore, GBS must be regarded as a serious disease. Plasma exchange (PE) and more recently high dose immune globulins (IvIg) have been proved to be succesful in shortening the duration of the disease, the duration of artificial ventilation and to improve outcome at 6 months (GBS study group, 1985; van der Meché et al., 1992; French cooperative group, 1992). In contrast to immune globulin therapy, plasma exchange is not always possible for haemodynamic reasons. In addition it is generally not feasible in children, not in all hospitals available, and is in general rather cumbersome. Therefore in the multicentre Dutch Guillain-Barré Study the effectiveness of immune globulins versus plasma exchange was evaluated in 150 patients, with a main aim to demonstrate at least equal efficacy. This study revealed therapeutic effectiveness of both therapies with a limited but significant superiority of immune globulins over plasma exchange (van der Meché et al., 1992).
In the Dutch Guillain-Barré trial each patient was tested electrodiagnostically three times in an early stage of the disease according to a rigid protocol. The results of these electrodiagnostic studies are the subject of this thesis.

Chapter one gives a review of the Guillain-Barré syndrome in particular with respect to symptoms and signs and the natural history of the disease. Also pathological, immunological and therapeutic features are reviewed briefly. Electrophysiological principles of nerve conduction in normal nerves and the electrophysiological features of demyelination are discussed in *chapter two*. They form the necessary background for the interpretation of motor conduction studies. According to these principles the protocol, which was designed for the present study, is presented along with the results of application in 45 healthy volunteers. The resulting limit values, applied in the present study are also presented. In *chapter three*, the literature concerning the electrodiagnostic aspects of GBS since 1960 is reviewed. In *chapter four*, electrodiagnostic findings in GBS patients in the Dutch GBS Study are described. Based on these results, the construction of electrodiagnostic criteria for polyneuropathy and for demyelination are worked out in *chapter five*. In *chapter six* the prognostic value of electrodiagnostic testing is described. *Chapter seven* describes aspects of axonal degeneration in the Guillain-Barré syndrome. Finally, *chapter eight* concludes this thesis with a general discussion and several suggestions for research in the near future.

Chapter one

The Guillain-Barré syndrome: an introduction

1.1 Terminology

The Guillain-Barré syndrome is a (sub)acute inflammatory polyradiculoneuropathy of unknown etiology. This condition was first described by Landry in 1859 (Landry, 1859) and Guillain, Barré and Strohl in 1916 (Guillain et al., 1916) and hence sometimes called Landry-Guillain-Barré-Strohl syndrome. Today, the disease is generally reffered to as Guillain-Barré syndrome or acute inflammatory demyelinating polyradiculoneuropathy (AIDP).

1.2 Epidemiology, antecedent events

True incidence in GBS probably varies in range from 1.5 to 2.0 cases per 100.000 annually (Alter, 1990; Arnason, 1993). These incidences are fairly constant for different geographical regions over the world. GBS occurs at all ages with two minor peaks in frequency: in young adults and in the fifth through eighth decade (Kaplan et al., 1983; Arnason, 1993). Most series have shown no seasonal preponderance to be present; usually GBS occurs sporadically but outbreaks have been reported (Arnason, 1993). In two thirds of the GBS patients an antecedent influenza-like syndrome with fever and in 10% to 20% an acute gastroenteric episode has been reported (Arnason et al., 1993). Usually, Cytomegalo virus, Epstein-Barr virus, human immunodeficiency virus, Mycoplasma pneumonia, Campylobacter jejuni and other infections, but also surgery, vaccination and malignant disease have been linked to GBS (Arnason, 1993). One to three weeks after the prodromal phase the first symptoms appear.

1.3 Signs and symptoms and natural history

Fifty percent of the patients reach their point of maximum deficit (nadir) within 2 weeks after onset and more than 80% respectively 90% within 3 and 4 weeks (Castaigne et al., 1966; Masucci and Kurtzke, 1971; Loeffel, 1977; Ropper, 1991). In the acute phase up to 5% of the patients may die (Loeffel et al., 1977; Ropper, 1991). After the acute phase, a plateau phase follows, with an average duration of 15 days (1 - 90 days) and in 71% 2 weeks (Ropper, 1991). Recovery is slower than the initial deterioration and after 4 to 6 months 80% of the patients have recovered satisfactorely; further recovery may continue even up to 2 years in severely affected patients with extensive axonal degeneration.

Prominent symptoms are quadriparesis, usually starting in the legs, occasionally, however, the disease begins with facial diplegia. Sometimes proximal muscle groups are more affected, but later distal weakness will predominate. The distribution of the weakness may be somewhat asymmetrical (Arnason, 1993). Intercostal and diaphramatic paresis may appear later in the disease. In at least 50% facial diplegia can be found. Oropharyngeal involvement may occur in 40% and may herald respiratory failure (Winer, 1985; Ropper, 1991). The external urethral sphincter is involved in 10% to 20%, however, incontinence is usually caused by overflow as internal sphincter function is spared. In the past respiratory failure has been an important cause of death, but today it can be managed by artificial ventilation. Objective sensory loss is present in 75% and pain in 55% of the patients (Ropper, 1991). Autonomic involvement may occur in a variety of ways; cardiovascular dysautonomies account for half of the deaths in GBS (Keenlyside, 1980). Areflexia is not always present initially, although the reflexes become abolished in the course of the disease (van der Meché et al., 1988a). Fifteen percent of the patients are left with permanent residual deficits, ranging from footdrop to wheelchair bound status and 5% of the patients remain more or less severely disabled (Pleasure et al., 1968; Winer, 1985; Ropper et al., 1986). De Jager reported that only one third of GBS patients, who needed artificial ventilation, recovered completely (De Jager, 1988).

1.4 Clinical criteria

Usually, the clinical diagnosis presents little difficulty. Several sets of criteria have been used in the past, particularly those of Masucci, Kurtzke and Ravn (Ravn, 1967; Masucci and Kurtzke, 1971). Today's established set is from Asbury et al. (see appendix I) (Asbury et al., 1978; Asbury and Cornblath, 1990).

1.5 Pathology and immunology

In the peripheral nerves of Guillain-Barré patients mononuclear cell infiltrates and segmental demyelination may be present throughout the whole extent of the nerve. Perivenular infiltrates of lymphocytes and macrophages are found. Areas of segmental demyelination are associated with lymphoid cellular infiltrates (Haymaker and Kernohan, 1949; Asbury et al., 1969; Kanda et al., 1989; Honavar et al., 1991; Arnason, 1993). Some nerves may be spared, for instance the sural nerve may lack cellular infiltrates (Brechenmacher et al., 1987; Hughes et al., 1992; Brown, 1993). No predominant involvement of motor- over sensory roots nor predominance of proximal over distal segments has been found. In recent studies, however, possibly some preference for proximal segments, extreme distal nerve twigs and usual compression sites exists (Arnason, 1993). The earliest change in the myelin sheath occurs paranodically, resulting in a widening of nodal gap. Demyelination progresses centripetally towards the center of the Schwanncell.

A second site of myelin breakdown occurs at the Schmidt-Lanterman incisura. Secondary axonal degeneration may be seen. Axonal involvement, however, may be so severe, that it has been questioned whether a primary axonal form of GBS exists (Feasby et al., 1986,1993; van der Meché, 1991a, 1991b,1994; Dijck, 1993; Brown, 1993). In lesions, which are several days to several weeks old, proliferation of Schwann cells occurs along denuded axons and also at sites, where axonal degeneration had taken place. Each denuded internode is replaced by several new thinner internodes. This process of repair begins already in the phase of demyelination (Arnason, 1993). Because of the pathological changes and the fact that GBS usually occurs within one or two weeks after an infection it has been held for long to be an immune mediated disease. This has been supported by the study of experimental allergic neuritis (EAN). Injection of crude myelin in combination with complete Freund adjuvant results in cell mediated demyelination in the rat and an antibody mediated demyelination in the rabbit. In the rat the glycoprotein P2 and in the rabbit galactocerebroside are identified as antigens. The same antigens are not or rarely involved in humane GBS (Hughes, 1991). Recently a pathological study has suggested, however, that in GBS in individual patients either a more cellular or more humoral mechanism may play a role (Honovar et al., 1991). This pathological variability may be the basis for the clinical and physiological variability observed (van der Meché et al., 1988a). Detailed concepts of the immune mechanisms in GBS have recently been described (Hartung et al., 1993; van der Meché and van Doorn, 1994). Peripheral blood T-lymphocytes expressing activation markers HLA-DR, the transferrin receptor and the membrane bound IL-2 receptor are increased. Furthermore, macrophages are activated in the early part of the disease. The aforementioned cells are most likely involved in antigen presentation in inflammatory foci. In a proportion of patients antibodies against peripheral nerve constituents do occur in the acute phase of the disease (Oomes et al., 1991). In our patientgroup 30% were shown to have antibodies against the ganglioside GM1. Also it was shown that 36% of the patients had a preceding infection with Campylobacter Jejuni. Subsequently, it has been demonstrated, that molecular mimicri may exist between specific strains of Campylobacter bacteria and GM1 ganglioside of the peripheral nerve (Oomes et al., 1992).

1.6 Therapeutic aspects

Although the Guillain-Barré syndrome is a self limiting disorder, 10 - 25% of the patients require artificial ventilation and up to 5% of the patients may die. Therefore an effective therapy has been searched for. Corticosteroids were among the first drugs tested (Shy and McEachern, 1951). Later trials were performed with prednison (Swick and McQuillain, 1971; Hughes et al., 1978). They did not result in a firm conclusion, but all studies had a small sample size. In a number of clinical trials the efficacy of plasma exchange has been evaluated (Greenwood et al., 1984; Osterman et al., 1984; GBS study group, 1985; French cooperative group, 1992). This therapy has proven to be effective in decreasing morbidity, including the

the duration of artificial ventilation and outcome at 6 months. As a result of the efficacy of high dose intravenous immune globulins in chronic inflammatory demyelinating polyneuropathy (CIDP) (Vermeulen et al., 1985; van der Meché et al., 1989), a pilot study was performed in the Guillain-Barré syndrome (Kleyweg et al., 1988). The results suggested that this therapy might be effective in Guillain-Barré syndrome. Immune globuline has several advantages over plasma exchange such as: general availability, few contraindications and easier management in children. For these reasons, the Dutch Guillain-Barré trial, a randomised multi-center study, comparing the effectiveness of intravenous immune globulin and plasma exchange in Guillain-Barré syndrome was performed. The main conclusion of this study was that in the acute Guillain-Barré syndrome, treatment with intravenous immune globulin is at least as effective as plasma exchange and may be superior (van der Meché et al., 1992). The major part of the EMG results are from patients in this study and a summary of the design of the trial is given below.

1.7 The Dutch Guillain-Barré trial

1.7.1 Entry into the trial

Patients were eligible if they fullfilled the criteria for acute Guillain-Barré syndrome (Asbury et al., 1978; Asbury and Cornblath, 1990), were not able to walk 10 meter independently, and could enter the study within two weeks of onset of neuropathic symptoms. The criteria for exclusion were: age less than four years, a previous period of Guillain-Barré syndrome, a previous severe allergic reaction to properly matched blood products, known selective IgA deficiency, pregnancy, treatment with immunosuppressive agents, severe concurrent other disease, or unavailability for follow-up during the next six months. Hereafter, randomisation for treatment was performed.

1.7.2 Treatment

After randomisation to plasma-exchange treatment was started as soon as possible; it was aimed to exchange 200 to 250 ml plasma per kilogram of bodyweight in five sessions within 7 to 14 days. Intravenous immune globulin was given during five subsequent days in a dose of 0.4 gram per kilogram bodyweight per day.

1.7.3 Assessment of motor function

The degree of motor function was expressed on a seven point functional scale used in previous trials, on which 0 denotes healthy; 1, having minor symptoms and signs but fully capable of manual work; 2, able to walk > = 10 m without assistance; 3, able to walk > = 10 m with a walker or support; 4, bedridden or chairbound (unable to walk 10 m with a walker or support); 5, requiring assisted ventilation for

at least part of the day; and 6, dead (Greenwood et al., 1984; Guillain-Barré study group et al., 1985).

1.7.4 Follow-up schedule

This functional score was measured at study entry and 16 times during six months of follow-up: 3 times a week during weeks 1 and 2, once a week through week 6, and in weeks 8,10,14,18,22 and 26. Of a total of 193 patients 150 patients entered the study from June 1986 through December 1989. Three of the 150 randomised patients proved to be ineligible soon after randomisation and were withdrawn from the study (unstable angina pectoris, transverse myelitis, Miller-Fisher syndrome). 73 patients underwent plasma exchange and 74 received immune globulin; their respective mean ages were 48.8 ± 19.2 and 46.2 ± 19.3 years.

1.7.5 Results

In the plasma-exchange group, 34 percent of the patients improved by one or more functional grades after four weeks, as compared with 53 percent in the immune globulin group; a difference of 19 percent (99 percent confidence interval, -2 percent to 39 percent; 95 percent confidence interval, 3 percent to 34 percent; P = 0.024). Hence it was concluded, that immune globulin was not only as effective as plasma exchange but that significantly more patients in the immune globulin group reached the main outcome measure of an improvement with one or more grades on the functional scale at four weeks after randomisation (van der Meché et al., 1992).

1.7.6 Electrodiagnostic studies

The Dutch Guillain-Barré study resulted in the availability of a large group of clinically well defined Guillain-Barré patients. The follow-up period of 6 months substantiated the clinical diagnosis further. Therefore this study was an unique opportunity to study the electrodiagnostic features of the disease. Three subsequent EMGs were performed at the time of randomisation and one and four weeks later. Electrodiagnostic testing was performed in temperature controled rooms or intensive care units, using standardised conventional techniques. Once the electrodiagnostic testprotocol had been designed, it was discussed with all participating centers before the trial was started (appendix II). Results were put on standardised data forms and sent to the study group coordination centre (appendix III). All tests were done by experienced clinical neurophysiologists, all members of the Dutch Guillain-Barré Study Group (appendix IV).

The following topics are the main aims of this thesis :

1. the description of electrodiagnostic findings in GBS in an early stage of the disease and the search for electrophysiological subtypes;

2. the construction of electrodiagnostic criteria for polyneuropathy and demyelination;
3. the evaluation of the prognostic value of electrodiagnostic testing;
4. the study of axonal degeneration in Guillain-Barré syndrome.

Chapter two

The technique and interpretation of motor nerve conduction studies

2.1 Electrophysiological aspects of nerve conduction in normal and in abnormal nerve fibers

The principles of the electrophysiology of normal conduction in myelinated fibers have been extensively elaborated in the past (Tasaki, 1953; Hodgkin, 1964; Katz, 1971; Keynes and Aidley, 1981; Kuffler et al., 1984; Kandel and Schwarz, 1985). A brief summary is given here.

At rest, an intracellular membrane potential of -60 mV with respect to the extracellular environment exists. This is maintained by an active process, whereby intracellular sodium is exchanged for extracellular potassium. This results in a relatively high intracellular concentration of potassium and a relatively low intracellular concentration of sodium relative to the extracellular environment. The membrane potential may change because of the presence of voltage dependent ion-channels, specifically permeable for these ions. At the node of Ranvier a high density of sodium channels and a natural lack of myelin exists: therefore the axon is only permeable for sodium-ions at this site of the myelinated axon. If at this site a depolarisation occurs beyond a certain threshold, voltage dependent sodium ion-channels will open. Because of the natural electro-chemical gradient, sodium ions will enter the cell. Being an influx of positive charge, further depolarisation and, in turn, further opening of voltage dependent sodium channels will result. The net effect is an explosive influx of sodium ions and a subsequent reversal of the polarity of the membrane potential: the action potential. This process comes to an end when a new equilibrium has been reached (+55 mV). At this point, sodium channels will close and potassium ion channels will open. The result is a restoration of the initial resting membrane potential. In this way the cycle of the action potential is completed. Due to this process an internal longitudinal current of positive charge is generated along the membrane. This positive current will decrease adjacent membrane potential and has therefore a depolarising effect. The current flows back via the external longitudinal current (local circuit). Normally, the internal longitudinal current is strong enough to depolarise the next node beyond the threshold for the generation of a new action potential. Even over a distance of two or three nodes a new action potential can be generated. The same cycle is repeated subsequently node after node. A jump like process is the result, the so called saltatory conduction, which is the hallmark of conduction in myelinated fibers. The latency, with which action potentials are generated from one node to the next is called the internodal conduction time, which determines the conduction velocity of a fiber. Internodal conduction time is proportional to the speed with which the internal longitu-

dinal current generated at one node has reached the threshold for action potential generation at the next node. The initial speed will be determined by the action potential rise time, which is a function of sodium ion channel kinetics in the nodal membrane. Furthermore, at the nodal membrane high membrane capacitance, low transmembrane resistance, and high intra-axonal resistance will diminish the speed (time constant) and the reach (length constant) of the depolarising effects of the internal longitudinal current. Low nodal membrane capacitance and high transmembrane resistance due to myelin are natural characteristics of myelinated fibers. They result in shorter internodal conduction time and hence in a high conduction velocity as well in a high safety factor. Large diameter fibers will have the fastest conduction, because of a smaller intra-axonal resistance. Obviously, changes in nodal as well as in internodal properties will have influences on conduction properties. Temperature has substantial effects on conduction, because it affects action potential generation. In particular, the rise time and duration of the action potential both decrease if the temperature of the nerve surrounding is higher. This results in a decrease of internodal conduction time and in decrease of the safety factor. Several decades ago, biophysical models have been developed for the description of action potentials as well as for conduction in normal nerve fibers (Hodgkin et al., 1952; Frankenhauser and Huxley, 1964; Rosenfalck, 1969).

Historically, Erb was the first to detect complete block in human traumatic peripheral nerve lesions using electrical stimuli. Muscle twitches could be observed by electrical stimulation of the nerve distal to the lesion but not proximal (Erb, 1876). Gombault decribed in 1881 segmental demyelination resulting from local traumatic lesions in man (Gombault, 1881).
However, the first systematic observations on conduction block in experimentally induced demyelination in cats -by local nerve compression- were done in 1944 (Denny-Brown and Brenner, 1944a, 1994b).
Tasaki induced demyelination by the application of saponin (a lipid solvent) to a single internode preparation of frog peripheral nerve. This resulted in an increase in internodal conduction time, which evolved in conduction block within 20 minutes. In addition, the specific electrical properties of the demyelinated internodal membrane could be derived. Compared to normal membrane increased capacitance and decreased transmembrane resistance were found (Tasaki, 1955). These experiments can be regarded as the first biophysical approach of the consequences of demeylination.
Local demyelination can be achieved by administration of diphteria toxin in the cat. In this way McDonald (1963a, 1963b was able to demonstrate conduction block as well as conduction slowing in whole nerve preparation from the recording of the compound nerve action potential, representing activity of a large number of fibers. Also in experimental allergic neuritis models, in which demyelination was induced by immunisation, it was possible to show these effects (Waksman et al., 1955; Keaser et al., 1962; Cragg and Thomas, 1964; Hall, 1967a, 1967b).
In experimentally induced focal demyelination resulting from direct micro-injection of diphteric toxin in the cat dorsal column, it was found that normal conduc-

tion on either side of stretches of demyelination were present and also that conduction can persist through smaller lesions, albeit with lower velocity (McDonald and Sears, 1970).
Rasminsky et al. were able to make a detailed study of internodal conduction between successive nodes of Ranvier in undissected spinal root fibers of the rat demyelinated by anti-galactocerebroside serum. They found that internodal conduction time may be increased up to 25 times of normal before conduction block occurs. This may be due to increased membrane capacitance and decreased transmembrane resistance, which both have an impeding effect on internal longitudinal current. Therefore, the depolarisation, which occurred at the next node of Ranvier was held to be insufficient to reach the threshold for the generation of an action potential (Rasminsky and Sears, 1972). These effects were found to be heavily dependent on temperature (Rasminsky, 1973), causing reversible conduction block in demyelinated fibers with small increases in temperature. Later, the introduction of electronic averaging techniques allowed the discovery of continuous conduction in completely demyelinated fibers accompanied by extremely slow conduction (Bostock and Sears, 1976, 1978; Bostock, 1993).
Saida and Sumner introduced acute antibody mediated conduction block in peripheral nerve fibers in the rat after intraneural injection of serum from galactocerebroside hyperimmunised rabbits (Saida et al., 1979, 1980; Sumner, 1981). Similar effects were found with serum from some GBS patients in some studies, but not in all (Sumner et al., 1982; Oomes et al., 1992). In an experiment performed by Lafontaine in rat single root fibers with anti-galactocerebroside serum, it was found that internodal conduction time and conduction block was associated with an increased nodal capacitance. Therefore they concluded, that acute conduction block in this model was due to paranodal demyelination (Lafontaine et al., 1982). This was in fact already predicted by computer simulation by Koles (Koles and Rasminski, 1972). Conduction block occurred earlier in smaller fibers (Sumner, 1981; Lafontaine et al., 1982). It was suggested that effects on conduction properties of the increased ratio of nodal to internodal capacitance would be greater in smaller fibers compared to larger diameter fibers.
Remyelination was extensively studied by Smith in lyso-phosphatidylcholine induced demyelination. Remyelination was accompanied by restoring of the normal safety factor and by near normal nerve conduction velocities. The newly formed internodal distances were shorter and the myelin sheats were thinner and therefore the transmembrane resistance lower (Smith and Hall, 1980; Bostock et al., 1981). Before remyelination, continuous conduction was followed by the development of nodelike patches along the demyelinated axon membrane, the so called phi-nodes (physiological nodes). They occured in the absence of remyelination 4 days after induction of the lesion (Smith et al., 1982a, 1982b). The phenomenon of phi-nodes has also been described by Feasby in regenerating small axons (Feasby et al., 1981). It is generally thought that this may represent regrouping of sodium channels (Smith et al., 1982b).

Conduction block is the most important consequence of demyelination. It may cause paresis and hypaesthesia. Demyelination may also result in ephaptic transmission and in spontaneous impuls generation. This may result in paraesthesia, dysaesthesia or even pain if present in sensory fibers and in fasciculations and myokymia if present in motor fibers. Other consequences of demyelination include increased internodal conduction time and continuous impulse propagation, both resulting in conduction slowing as well as reduced ability to transmit a train of impulses (Rasminsky and Sears, 1972; Smith and Hall, 1980; McDonald et al., 1982), which may also add to paresis. Conventional electrodiagnostic studies can only reveal conduction slowing and conduction block. Advanced techniques are necessary to detect spontaneous impulse generation (Hagbart, 1979).

2.2 Technique and interpretation of motor nerve conduction studies

Introduction

Motor nerve conduction studies are helpful in the diagnosis of peripheral neuropathies. They have become even more important now several demyelinating polyneuropathies such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy (MMN) can be treated by immunomodulating therapies like IvIg, PE, corticosteroids and cytotoxic drugs (Guillain-Barré syndrome Study Group, 1985; Vermeulen, 1985; Pestronk et al., 1988, 1990; van Doorn et al., 1990, 1991; Nobile Orazio et al., 1990a, 1990b; French cooperative group, 1992; van der Meché et al. 1992). It is the only method to discriminate between motor neuron disease and MMN with persistent conduction block, the distinction of which has obvious implications for management (Lewis et al., 1982; Pestronk et al., 1988; Nobile Orazio et al., 1990a). However, limiting nerve conduction studies to the measurement of nerve conduction velocities, may erroneously suggest normal nerve function. It is a well known fact, that quadriparetic Guillain-Barré patients may show normal conduction velocities (Lambert, 1960; Brown and Feasby, 1984; Albers, 1985; Ropper, 1991). As will be elaborated below this is mainly due to the fact that blocked fibers may go undetected with this approach. Motor nerve conduction studies may, however, be extended by simple measurement of amplitude and duration of the responses in order to obtain more information about nerve function, particularly conduction block and abnormal dispersion (Lambert, 1960; Sumner, 1981; Brown et al., 1981; Brown and Feasby, 1984; Brown, 1984; van der Meché, 1988a; Brown and Bolton, 1993). This chapter introduces the electrophysiological background of motor nerve conduction studies. The technique and interpretation of motor nerve conduction studies and in particular CMAP measurement, will be discussed. The application in several specific polyneuropathies will be reviewed and a protocol for further studies will be proposed.

2.2.1 Electrophysiological background of motor nerve conduction studies

After stimulation of a motor nerve, contraction of the appropriate muscle will occur. If electrodes are attached to the skin over the muscle belly a Compound Muscle Action Potential (CMAP) can be recorded (fig. 1a). The CMAP is the summation of motor unit potentials (MUP's) generated by, numerically few, large motor units of which the axons are synchronically activated by the stimulus (Brown et al., 1984). However, despite the fact that nerve fibers are activated in a synchronised manner, there is no such strict synchrony of the generated respective MUPs, because of differences in conduction velocity of the individual nerve fibers. In addition, differences in latencies are also due to the fact that, motor end plates are not in line, but, instead are scattered with regard to the recording electrode. As a result, electrical positive phases of one MUP will occur at the same time as negative phases of another MUP. The net effect is that a number of MUP's will cancel out each other, because of summation of electrical positive and negative phases. Because of this phase cancelation the CMAP is not simply the algebraic summation of all positive and negative phases of the MUP amplitudes (fig. 1b). Phase cancellation will be more pronounced if the distance between stimulation site and muscle increases, because naturally occurring differences in conduction velocities will augment the shift of MUPs in time. This effect is called temporal dispersion (fig. 1c) and is even stronger in sensory nerve compound action potentials due to the very short duration of the sensory fiber potential compared to the MUP (Kimura et al., 1986, 1988). Several authors regard a CMAP amplitude reduction up to 50% in the segment of the forearm due to phase cancellation possible in healthy individuals. Therefore, they advocate the use of CMAP area as a parameter, since this parameter shows less but still considerable reduction in healthy individuals (fig. 1b) (Kimura et al., 1986; Kimura, 1988; Rhee et al., 1990).

CMAP configuration is further influenced by motor end plate function and muscle fiber architecture. Also it is important to realise that MUPs generated further away from the recording electrode will contribute less to the CMAP compared to nearby MUP's. Therefore, the CMAP amplitude is only an indirect indicator for the number of functionally intact nerve fibers between stimulation site and the muscle recording site. However, if a motor nerve is stimulated at several sites along its length, CMAP amplitudes evoked at more proximal sites will decrease only with a small percentage as is evident from observations in most healthy individuals (fig. 2a)(see reference values in appendix V). Therefore this technique is very efficient in testing the integrity of the motor nerve over considerable distances of the peripheral nerve.

The onset latency of the CMAPs is used for computing motor nerve conduction velocity (fig. 1b). Onset, however, represents only the fastest conducting motor fibers. Nerve conduction velocity computed in this way is therefore "the maximal conduction velocity" and, as a consequence, many fibers in a nerve may become slowed without any effect on the maximal conduction velocity as long as the

fastest fibers remain intact. To overcome this limitation one may measure the degree of dispersion - i.e. the duration of the negative phase - of the CMAP (see below).

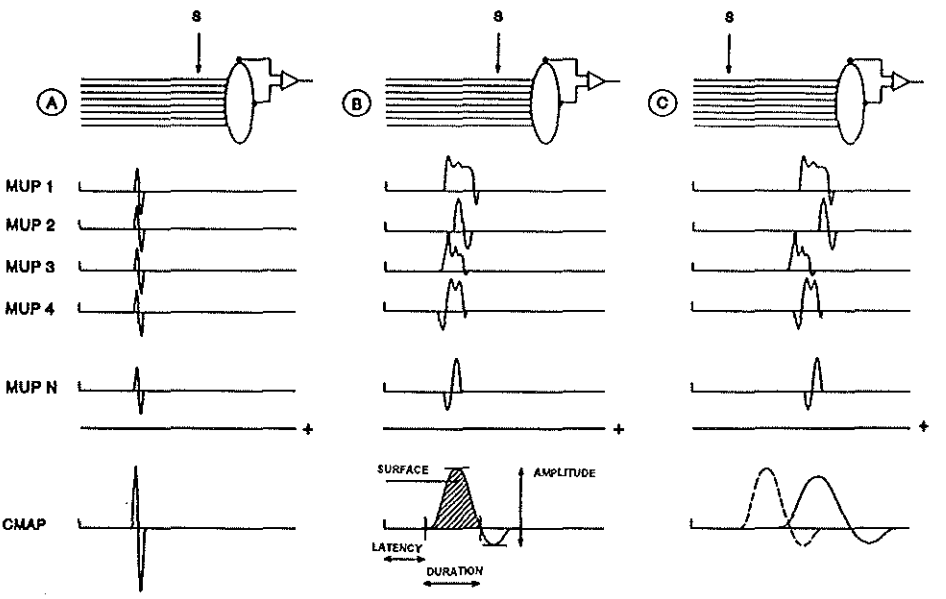

Fig. 1. Summation of MUPs into the CMAP.
Diagram of peripheral motor nerve stimulation with resulting CMAP. Each of the 8 horizontal lines represent a large group of motor axons, innervating the muscle. Above the muscle, surface electrodes are attached in the "tendon-belly montage" and are connected to the recording apparatus at the right hand side. The vertical arrow indicates the stimulus site.

a. Summation of MUPs into a CMAP. MUPs with similar configuration cause no phase cancellation and result in an unrealistic CMAP configuration with high amplitude and small duration.
b. MUPs with characteristic diverse configuration cause phase cancellation and result in a more realistic CMAP configuration with lower amplitude and larger duration. CMAP parameters: onset latency; amplitude; surface of negative part; duration of negative part of the CMAP are indicated.
c. as in b. with more proximal stimulation. As a consequence of normally occurring differences in NCVs of different motor axons, the generation of MUPs is less synchronised, which resuls in a lower and broader CMAP configuration, compared to distal stimulation. CMAPs of b. and c. are shown in superposition.

2.2.2 Effects of demyelination and axonal degeneration on motor nerve conduction

Abnormal results in conduction studies may be caused by damage to myelin sheath or axon. Although these phenomena tend to occur simultaneously, we will discuss the effects separately.

2.2.2.1 Abnormalities of the myelin sheath

The physiological consequences of demyelination are primarily conduction block and conduction slowing (Lambert, 1960; McDonald, 1963b; Sumner, 1981; Lafontaine et al., 1982; Brown et al., 1984; Feasby et al., 1985; Albers et al., 1985; Albers and Kelly, 1989) .

Conduction block between stimulation site and muscle in a number of fibers will result in a decreased CMAP amplitude on stimulation proximal of the lesion (fig. 2b). A normal CMAP may still be obtained on stimulation distal of the lesion. Stimulation proximal of the lesion in case of conduction block in all fibers will not give any response (fig. 2c). In contrast, if the axons are injured e.g. by transsection axons in the distal stump can be normally activated initially (fig. 2d). In a period of days, neither stimulation distally nor proximally will cause a response, because all nerve fibers distal to the lesion have undergone Wallerian degeneration and are not excitable anymore (fig. 2e).

If demyelination and thereby conduction block is diffusely present over the length of a nerve, CMAPs become progressively smaller with more proximal stimulation (fig. 2f). This may be a typical finding in some patients with acquired demyelinating polyneuropathy as in GBS and CIDP. The essence is, therefore, that stimulation distal to a demyelinating lesion gives a normal response, whereas stimulation proximal to the lesion produces a decreased response in the muscle. Because the CMAP is the only means to detect conduction block, it is obvious that meticulous testing of CMAPs is essential to the diagnostic evaluation of neuropathies.

Slowing of nerve conduction can be the result of different pathophysiologic mechanisms as reviewed by Waxman (Waxman, 1977, 1980). In saltatory conduction, the action potential jumps from node to node. The time needed is called the internodal conduction time. In addition, the time needed for action potential generation at a node also adds a certain delay. As a consequence, the internodal conduction time, as well as the number of nodes passed by the action potential, will determine the final conduction velocity of a fiber. Internodal conduction time is prolongued and finally blocked by less efficient nodal depolarisation. This may be due to decreased resistance at the internode and increased capacitance at the node caused by internodal and paranodal demyelination. In complete demyelination the now continuous propagation will result in a very slow conduction. Conduction slowing in patients, recovered from a neuropathy, is probably best explained by an increase in the number of Ranvier nodes after remyelination.

After repeated de- and remyelination, nerve conduction velocities of individual nerve fibers within a nerve may diverge widely. This causes *abnormal temporal dispersion* in MUP latencies after stimulation of the nerve and results in a *longer duration* of the CMAP waveform. In addition, the resulting increase in desynchronisation of the constituent MUPs of the CMAP will result in an increase in phase cancellation, so, in turn, the amplitude of the CMAP will decrease. As this phenomenon will be stronger with more proximal stimulation, it may simulate conduction block. However, in contrast to CMAP reduction by conduction block,

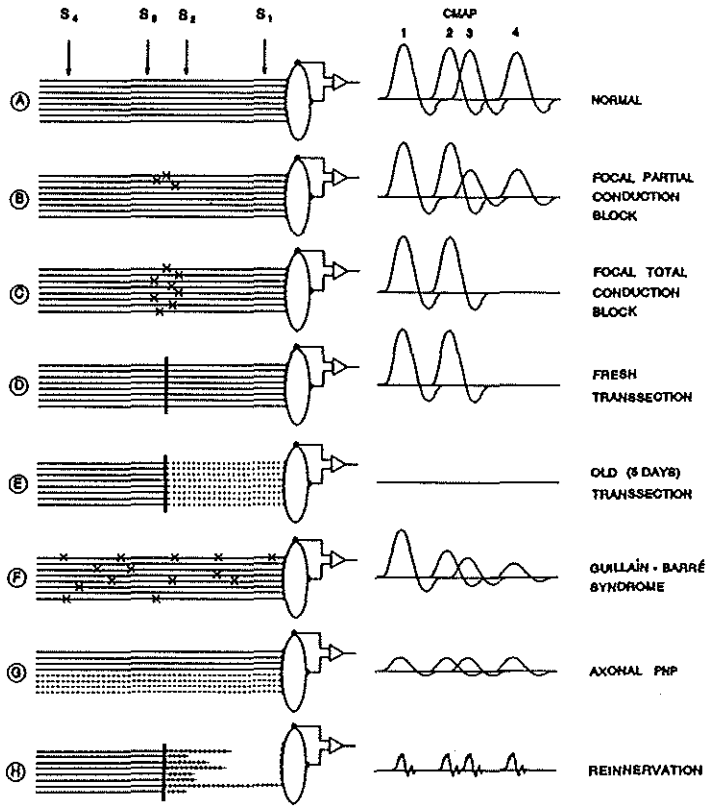

Fig. 2. Effect of conduction block, axonal degeneration and reinnervation on configuration of distal and proximal elicited CMAPs.

Diagram as in fig. 1. Arrows 1 to 4 represent progressively more proximal stimulation. At the righthand side the respective motor responses (CMAPs) shown in superposition. The CMAP resulting from most proximal stimulation is at the far right. Hatches indicate conduction block. Dashed lines indicate axonal degeneration; short dashes indicate reinnervation. The vertical bar represents a transection.

a. normal nerve conduction: slight CMAP reduction after more proximal stimulation due to normal temporal dispersion;
b. focal partial conduction block: lower CMAPs on stimulation proximal of the lesion;
c. focal complete conduction block (neurapraxia): total abolished CMAPs proximal of the lesion;
d. transection (neuronotmesis): normal CMAPs distal to the lesion;
e. transection with completed Wallerian degeneration in the distal stump (after 5 days): abolished CMAPs on any stimulation site;
f. diffuse conduction block: length dependent CMAP amplitude reduction as may occur in GBS;
g. axonal degeneration as in axonal neuropathies: low CMAP amplitudes on any stimulation site;
h. reinnervation as in traumatic nerve injuries: low polymorph CMAPs.

abnormal temporal dispersion will also cause a broad CMAP waveform (fig. 3). To estimate conduction block it is, therefore, important to appreciate CMAP duration.

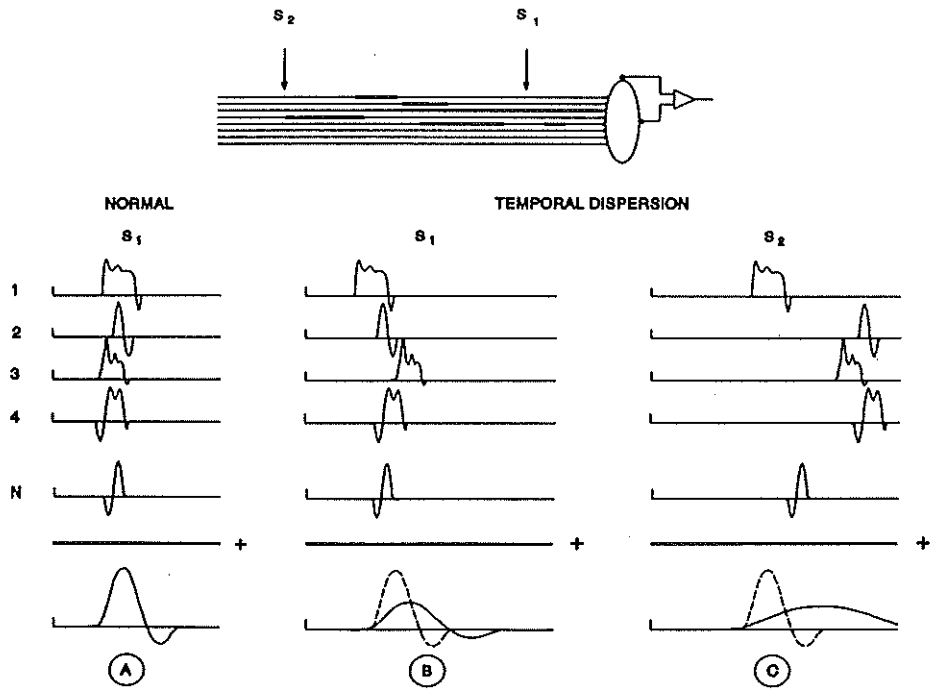

Fig. 3. Abnormal temporal dispersion.
As a consequence of non-uniform conduction slowing in several motor axons some MUPs are very delayed (traces 4, n). This results in an abnormal low and broad CMAP waveform as compared to the CMAP in the normal situation. More proximal stimulation further augments this phenomenon.

A rather uncommon, but important finding in some polyneuropathies is a *changed electrical excitability.* Fibers, that are conducting normally may in these cases be difficult to stimulate electrically. This phenomenon is probably best explained by interstitial edema in the nerve or by changes in the myelin architecture. Decreased CMAP amplitude due to hypoexcitability may form a pitfall, that can be checked for by sufficiently increasing stimulus strength. This will result in the recruitment of more fibers and hence in increased CMAP amplitude. In our experience decreased electrical excitability occurs frequently in chronic demyelinating neuropathies.

2.2.2.2 Abnormalities of the axon
After section of a nerve, conduction is abolished distally of the lesion due to Wallerian degeneration, however, it will take approximately five days before this process is completed (Chaudry et al., 1992). Therefore conduction studies can only distuingish axonotmesis and conduction block only after a 5 day interval (fig. 2d

and 2e). In axonal neuropathy, nerve conduction velocities are often preserved or found to be slightly diminished only. It is explained by the fact that some of the thick fast conducting axons may be preserved. Slowing of conduction will occur, if thick axons are lost or have become thinner by atrophy (Waxman, 1977, 1980). Since in axonal polyneuropathy motor units are lost, the CMAP amplitude will be lower than normal, independent of the level of stimulation along the nerve (fig. 2g). After regeneration and reinnervation, particularly in case of traumatic nerve injuries, axons may be very thin and as a consequence, conduction may be very slow, leading to excessive dispersion. This in turn causes phase cancelation and the result will be a low and irregular CMAP wave form (fig. 2h).
In conclusion, by studying CMAP related parameters (amplitude and duration), conduction velocity and excitability, nerve conduction properties can be characterised. By stimulating the nerve at several sites along its length, it is possible to test different nerve segments for conduction properties. The use of these variables as guidelines for electrodiagnostic evaluation in polyneuropathy are proposed. Limit values were obtained in 45 healthy volunteers (appendix V). In the next section, we will briefly discuss the technique and interpretation of electrodiagnostic findings.

2.2.3 Technique and interpretation

2.2.3.1 CMAP amplitudes

Nerve conduction studies are performed using surface electrodes in the "tendon-belly montage", attached over the muscle belly. In this setting it is possible to search with the active electrode for the position in which an optimal CMAP can be obtained from the muscle innervated by the nerve in study (fig. 4A,1). The CMAP then shows the maximal amplitude, steepest and initial negative deflection and smallest duration of its negative phase as possible. One has to be alert for electrical shortcuts between the electrodes by electrode paste, for this lowers the recorded CMAP dramatically (fig. 4A,2). This approach may seems tedious, but significant changes in CMAP configuration with more proximal stimulation may offer important diagnostic clues.

If similar *low CMAP amplitudes are found after distal and proximal stimulation* of the nerve one has to check first for inappropriately placed electrodes or electrode artifacts such as moist bridges (fig. 4A). If the CMAP amplitude grows further after increasing stimulus strength above usual levels, incorrect stimulus position is possible and searching for the optimal stimulus site by shifting the stimulating electrodes is necessary (fig. 4A,3). If a number of fibers have a higher stimulus threshold, this population will not be activated with the usual stimulus strength. This will also result in a lower CMAP but is not caused by conduction block or fiber loss (see below). If artifacts are ruled out and the nerve does not show signs of lesser excitability, lower CMAPs may point to axonal degeneration (amyotrophic lateral sclerosis (ALS), radiculopathies, axonal neuropathies) (fig. 4B,1), very distally located demyelination (e.g. demyelinating neuropathy) (fig. 4B,2) and

neuromuscular transmission block (Eaton-Lambert syndrome) (fig. 4B,3). Caution is necessary in interpreting absolute values as normal ranges may be quite broad, for instance the normal range for hypothenar CMAPs is 15 mV to 30 mV.

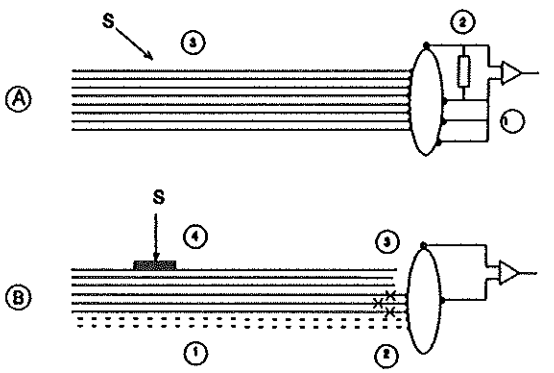

Fig. 4. Causes of low CMAP amplitudes.
Causes of low CMAP amplitudes include artifacts (A1. inappropriately placed recording electrodes; A2. moist bridges; A3. inappropriately placed stimulus electrodes) and pathophysiological factors (B1. axonal degeneration; B2. distal conduction block; B3. Eaton-Lambert syndrome; B4. decreased excitability).

If a *higher CMAP is found after proximal stimulation* anomalous innervation has to be ruled out. A well known example is an accessory peroneal nerve to extensor digitorum brevis muscle. Another pitfall may occur if more than one nerve is activated at sites where nerves are not far apart as in the bicipital sulcus or at the wrist. The recording electrodes can then unintentionally be influenced by a CMAP from another muscle. A higher and changed CMAP waveform after proximal stimulation is very suspect for these phenomena.

If *CMAP amplitudes are lower after proximal stimulation* several possibilities have to be considered before concluding that it is caused by conduction block. Anomalous innervation, for instance median to ulnar (Martin-Gruber) anastomosis may also be an underlying cause (Oh, 1992) . Several strategies are possible to rule this out (Kimura, 1984, 1989). In anomalous innervation CMAP waveforms change after proximal stimulation as compared to distal stimulation. Another cause of error may be a shifted recording electrode position induced by movements during successively more proximal stimulation. This can easily be checked by repeating the distal stimulation and comparing it with previous results. Finally one has to be sure that the stimulus strength was really supramaximally, since more proximally the nerve may be burried deeper in the tissue.

Conduction block and temporal dispersion

If, in distal to proximal CMAP amplitude reduction, anomalous innervation has been ruled out and the nerve has been stimulated supramaximally, conduction block in the nerve segment between distal and proximal stimulation sites is very probable (fig. 2b). It is important to search for focal conduction block outside usual compression sites in a patient suspected of motorneuron disease, since this is the only method to discriminate from multifocal motor neuropathy, which needs an essentially different clinical strategy.

Amplitude reduction in the absence of conduction block will occur if abnormal strong phase cancellation is present. This effect may be suspected if the duration of the CMAP is abnormally increased with more proximal stimulation compared to distal stimulation. This is called temporal dispersion. This will lead to broad, polymorf and low CMAP waveforms, which can be easily recognised (fig. 3b).

It is not always possible to separate conduction block from phase cancellation as a cause of CMAP amplitude reduction. It is, however, important to state here, that both conduction block and differential temporal dispersion are phenomena related to demyelination; for diagnostic purposes it is not necessary to distinguish between the two. Only conduction block, however, is related to clinical deficit (van der Meché et al., 1989) . An attempt to distinguish between the two was made by Brown and Feasby (Brown and Feasby, 1984) . They suggested that if amplitude reduction exceeds 20% and if increase of duration of the negative phase of the CMAP does not exceed 15%, the amount of interphase cancellation is supposed to be small and the presence of conduction block is more likely the cause of CMAP amplitude reduction. In contrast if duration of the CMAP increases more then 15% with proximal stimulation, then amplitude reduction by interphase cancellation cannot be distinguished from conduction block. Several sets of electrodiagnostic criteria for primary demyelination have been constructed in recent years (Albers and Kelly, 1989; Barohn et al., 1989; Asbury and Cornblath, 1990).

2.2.3.2 Nerve conduction velocities (m-NCV) and distal motor latencies (DML)

Conventionally, m-NCVs are computed by dividing the distance between sites of stimulation with differences in CMAP onset latency. Onset latency, however, is the earliest component of the CMAP, which is elicited by the fastest conducting motor fibers. Therefore, only the so called maximal m-NCV (usually just called m-NCV) can be obtained, which represents obviously only a smal contingent of motor units. Distances between stimulus sites at the skin are measured using a measuring tape or a pair of calipers. However, these points do not necessarily correspond with the site where the nerve fibers are actually depolarised (the so called virtual cathode). Moreover, additional inaccuracies in measuring distances will occur with deeply sited nerves with winding stretches, as for instance in the radial nerve across the spiral groove.

Lower temperature of the nerve surrounding will cause a decrease in NCV. To minimise unwanted bias in conduction velocity from variation of temperature, one option is to warm up the limbs up to 30° Celsius. However, it is not always possible to apply this cumbersome procedure, particularly in the intensive care unit.

Other approaches are transforming measured values (distal motor latency and NCV) for a deviation of the standard temperature of 35° Celsius or to apply limits of normal dependent on temperature. In our laboratory, we prefer transformation of DML and NCV values, because skin temperature corresponds well with nerve temperature (DeJesus et al., 1973; Geerlings and Mechelse, 1985). Warming of the limb will certainly cause an increase of nerve temperature, however only after an unknown interval, which may introduce unpredictable results.
Conduction slowing can be caused by several different mechanisms due to changes in architecture of myelin sheath or axon membrane. Examples in demyelination are: increased internodal conduction time, continuous conduction and an increased number of shorter internodes. An example of axonal causes is reduction of axonal diameter in atrophy.
Hence, conduction slowing is a rather unspecific indicator of nerve dysfunction. Only a strong reduction in m-NCV (more then 70%) is a generally accepted characteristic of demyelination (Lambert, 1960; McDonald, 1963b; Kelly, 1983; Albers et al., 1985; Albers and Kelly, 1989; Brown and Bolton, 1993).
Motor-NCVs do not necessarilly correlate with clinical motor status because weakness is either caused by conduction block or axonal loss. Striking examples of the discrepancy between slow conduction and clinical deficit came from demyelinating polyneuropathies. In the acute GBS often near normal NCVs are present in quadriparalytic patients, because of a small number of still normally conducting fibers. In contrast, very low motor nerve conduction velocities (e.g. 20 m/s) may be found in patients who are able to walk because little conduction block is present. This may be seen in patients suffering from HMNS type I (HMSN) or CIDP.
It is not possible to compute m-NCVs in the distal part of the nerve. Not only is it difficult to measure distances accurately, also conduction is not a homogeneous process. The terminal motor twigs become thinner and therefore conduction velocity decreases. Finally, synaptic delay occurs at the motor endplate. Therefore, conduction in the final part of the nerve is simply given as the DML; it is often prolonged in demyelinating polyneuropathies.

2.2.3.3 Excitability
In routine nerve conduction studies, it is a prerequisite to stimulate the nerve supramaximally, i.e. twice the minimal stimulus strength needed to elicit a maximal CMAP amplitude (i.e twice the stimulus threshold). In normal nerves, this threshold is reached by rather small electrical stimuli if conventional surface stimulation electrodes are applied (e.g. 0.3 msec. duration and 10 mA). By definition, CMAPs will not further increase in amplitude if stronger stimuli are applied. However, in some nerves the threshold is far beyond that of normal nerves. Therefore, in such cases, stimulus strength has to be augmented until the CMAP amplitude does not grow further. If not recognised, this phenomenon may give rise to major pitfalls in CMAP amplitude measurement (fig. 4B,4). Particularly, where nerves are deeply situated, which is usually the case for proximal stimulation sites, it may give rise to falsely low CMAP amplitudes mimicking conduction block. In our experience

excitability is often changed in CIDP and HMSN type I and sometimes in GBS in the post-acute phase.

2.2.4 Motor nerve conduction studies in clinical practice; some guidelines

In addition to motor nerve conduction studies other electromyodiagnostic tests like sensory nerve conduction studies and needle electromyography may be indicated. With these techniques the electrodiagnostic characteristics of several neuropathies can be evaluated. These are summarised in table 1.
In practice, one has to chose which nerves are to be tested. The clinical findings and the condition of the patient determine the choice of the number and kind of nerves to start with. The findings in the initial part of the investigation will further determine the strategy.
For screening purposes, testing of one nerve in the upper- and lower extremity is minimally required. In the upper extremity the ulnar nerve is preferably tested. Due to its superficial position over an extensive length this nerve is easily accesible for tracing focal conduction block. This nerve can be stimulated stepwise by moving the electrode inch by inch over its entire length between wrist and axilla. This procedure is therefore called "inching". CMAPs are recorded from the hypothenar (abductor digiti quinti). An advantage is that this muscle is far apart from the thenar muscles, so that volume conducted thenar CMAPs, elicited by unintentionally stimulated median nerve fibers, will have minor or no influence on hypothenar CMAP. In the lower extremity the peroneal nerve is very suitable and in case of muscle fiber degeneration of the extensor digitorum brevis the posterior tibial nerve is a good alternative. CMAPs can then be recorded from muscles in the sole of the foot.

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Table 1. Electrodiagnostic characteristics of several neuropathies.
Characteristically increased (↑), decreased (↓), unchanged (=); the sensitivity and specificty have not always been determined. If characteristic changes are possible, but not usually present this is indicated with the =/ sign.

GBS: Guillain Barre syndrome; CIDP: Chronic Inflammatory Demyeliniting Polyneuropathy; HMSN I: Hereditary Motor Sensory Neuropathy (demyelinating type); MMN: Multifocal Motorneuropathy with persistent conduction block; DML: Distal motor latency; m-NCV: Motor nerve conduction velocity; reduction: reduction of CMAP amplitude after proximal compared to distal stimulation; duration: duration of negative part of CMAP; =: unchanged; *: all characteristics tend to be focal.

Table 1. Characteristic changes in electrodiagnostic parameters in several neuromuscular disorders.

	DML	m-NCV	distal CMAP amplitude	reduction of CMAP amplitude	duration of CMAP	excitability	sensory amplitude	ref.
GBS	↑	=/↓	↓	=/+	=/↑	=/↓	=/↓	i
CIDP	↑	↓↓	↓	=/+	↑	↓	↓	ii
HMSN I	↑	↓↓	↓	=	=	↓	↓	iii
Axonal pnp	=	=/↓	↓	=	=	=	↓	iv
Motor neuron disease (ALS)	=	=/↓	↓	=	=	=	=	v
MMN	=	↓	↓	*↓	=	=	=	vi
Critical illness pnp	=	=	↓	=	=	=	↓	vii

i (Lambert, 1960; Brown, 1984a; Albers, 1985; van der Meché, 1988a)
ii (Lewis, 1982b; van der Meché, 1989; Dijck, 1993b).
iii (Lewis, 1982b; Dijck, 1993a)
iv (Donofrio, 1990)
v (Bradley, 1987)
vi (Lewis, 1982a; Krarup, 1990; Pestronk, 1988; Parry, 1993)
vii (Bolton, 1986; Zodochne, 1987)

If no abnormalities are found in routine electrodiagnostic testing, the number of nerves has to be extended and proximal parts may be included by the study of late responses. Late responses such as F-responses are only relevant for the study of nerve conduction velocities. Their absence is no proof for proximal conduction block since they are not always present in healthy subjects and evoked F-responses may be blocked in distal segments if the distal CMAP is reduced due to distal demyelination or dying back axonal neuropathy. Conduction block, confined to very proximal sites is difficult to detect. Although it is conceivable to stimulate the ventral roots, supramaximal stimulation was proved in our lab to be unreliable both for magnetical as electrical stimulation.

In conclusion: careful CMAP measurement is a necessity for adequate electrodiagnostic testing in addition to conventional conduction velocities. It is the only reliable way to detect conduction block and temporal dispersion, both important electrodiagnostic signs of demyelination. Using the guidelines presented it is easy to avoid the majority of technical pitfalls.

Chapter three

Electrodiagnostic tests in the Guillain-Barré syndrome, a review of the literature since 1960

3.1 Historical perspectives

In his original report, dating from 1960, Lambert (Lambert, 1960) described a Guillain-Barré patient, whom he tested electrodiagnostically 14, 27 and 81 days after onset of the disease. On distal stimulation of the median, ulnar and peroneal nerve he found a normal CMAP. With more proximal stimulation, however, he found evidently lower amplitudes (CMAP-reduction). He ascribed this phenomenon to conduction block. Therefore this author may be regarded as the first one to formulate the concept of length dependent CMAP amplitude reduction, which has since proven to be the most typical electrodiagnostic sign in demyelinating polyneuropathy. In addition he found only slightly reduced conduction velocities in early stages of the disease (fig. 5).
Many electrodiagnostic studies in GBS have been performed since. However, the fact that CMAP amplitude reduction, reflecting conduction block, as a cardinal sign in GBS, was not appreciated generally until the early 80s. One exception, however, can be found in a study by McQuillen (McQuillen, 1971). Surprisingly enough, these authors did not comment on the importance of this finding.
In 1964 McDonald performed electrophysiological and morphological studies in artificially induced demyelination on an animal model (McDonald, 1963a, 1963b; McDonald et al., 1982). It was not until similar studies had been performed in the early eighties (Antigalactocerebrosidase serum model:(Lafontaine et al., 1982) EAN model:(Saida et al., 1979; Sumner et al., 1982; Hahn et al., 1985;), AIDP serum model: (Feasby et al., 1982; Harrisson et al., 1984), that reports started to appear on the nature and pathophysiological backgrounds of electrodiagnostic findings in peripheral nerves in the human (Sumner, 1981; Brown et al., 1981, 1984; Feasby et al., 1985). These reports led to re-appreciation of the CMAP and stressed the importance of measuring CMAP amplitudes for the assessment of conduction block in patients with demyelinating polyneuropathy.

3.2 Nerve Conduction Studies

The occurrence of *normal nerve conduction velocities* in GBS patients has been reported frequently (Lambert 1964: in 14%; Humphrey 1964; Bergamini 1966; McQuillen 1971: in 41%; Eisen 1974: in 5%; Mcleod 1976: in 14%; Raman,1976: in 13%; McLeod 1981: in 9%; Niewiadomska 1981: in 57%; Brown,1981,1984 in the majority of their patients; Walsh,1984; Albers 1985; Ropper 1990). McLeod

(1981) stressed the fact that in one patient nerves with normal and abnormal conduction can be found simultaneously (McLeod, 1981).

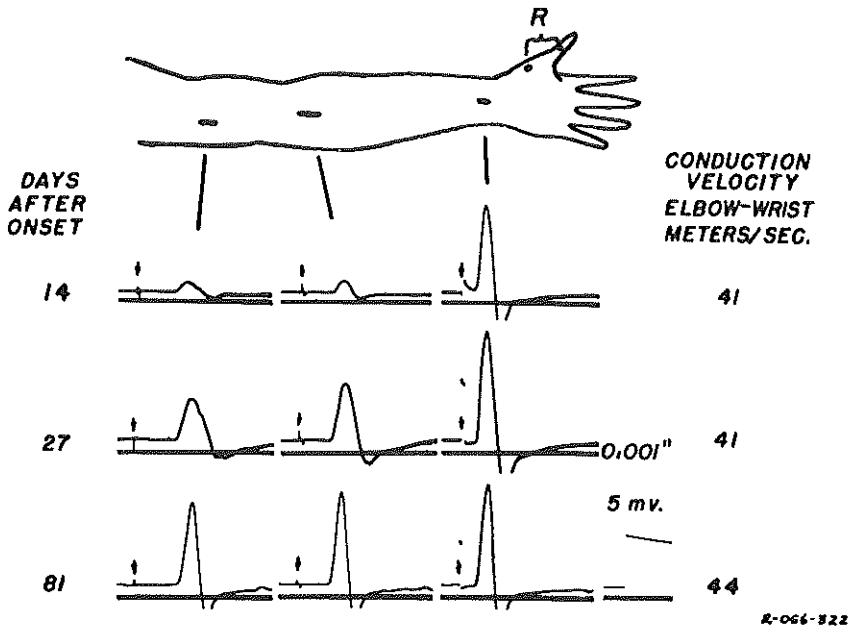


Fig. IX.7. Guillain-Barre syndrome. Action potentials of the abductor pollicis muscle evoked by maximal stimulation of the median nerve in the upper arm, at the elbow and at the wrist. *R.* is the recording site. Tests were made 14, 27, and 81 days after acute onset of the disease. At 14 days, although the patient was quadriplegic, stimulation of the nerve at the wrist evoked an essentially normal response from the muscle, indicating that wallerian degeneration had not occurred. There was little or no evidence of fibrillation on needle electrode examination of the muscle. Strength-duration curves were normal. Stimulation of the nerve at the elbow and upper arm evoked only a small response from the abductor pollicis muscle indicating failure of excitability and/or conduction of the majority of motor fibers to this muscle in the more proximal part of their course. With time, conduction returned in the proximal part of the nerve. The distal part of the nerve remained excitable. Recovery of the response to stimulation at the elbow began earlier and occurred more rapidly than recovery of the strength of voluntary contraction. A similar sequence of events occurred in the ulnar and peroneal nerves.

Fig. 5. Lambert's Guillain-Barré patient (Lambert, 1960).

Conduction slowing was found by Lambert (1964) in 61% of his patients (NCV below 70% of the normal mean). Most pronounced slowing was found at usual compression sites and in 25% a prolonged DML was detected (Lambert and Mulder, 1964). McLeod (1976,1981) found conduction slowing in 49% of their patients (upperlimb nerves below 40 m/s and in peroneal nerve below 40m/s) (McLeod et al., 1976, McLeod 1981). Brown (1964) reported abnormal DML in 30% and slowed m-NCV in 13% in 46 patients, which were tested within 2 weeks after onset of motor symptoms (Brown et al., 1984). Cornblath tested 210 patients

electrodiagnostically (50% were tested within 10 days and more then 75% within 15 days after onset); 24% had abnormal m-NCV and 40% had abnormal DML (Cornblath et al., 1988). In a prospective study, 25% of the patients had slowing in an early stage in at least two nerves (Ropper et al., 1991).
In a serially tested group of GBS patients, particularly prolongued DML and lower CMAP and in lesser extent slowed m-NCVs were found within one week of onset (Rudnicky et al., 1992) .
In addition, several authors found prolongued DML in the presence of normal or near normal conduction velocity in more proximal segments (Bannister and Sears, 1962; Isch et al., 1964; Bergamini et al., 1966; McQuillen, 1971; Eisen et al., 1974; Kimura, 1975; Kimura and Bosch, 1975; McLeod et al., 1976; McLeod, 1981).
Comparison of sensory versus motor nerve conduction velocities.
Eisen (1974) found that compound sensory nerve action potentials (CSNAP's) were absent in ulnar and/or median nerve in 58%, and McLeod found sensory nerve conduction abnormalities in 76% of their patients (Eisen et al., 1974; McLeod, 1981). Ropper found normal sensory conduction in two or more nerves in 37% of 107 patients (Ropper et al., 1985). Predilection for motor over sensory abnormalities were also described (Eisen et al., 1974; McLeod, 1981). In a retrospective study Albers (1986) found a consistent predominance of motor over sensory abnormalities at all stages of the disease (e.g. in 88% and 25% of the patients, respectively, in the first week). Particularly sural nerve conduction was normal in contrast to motor nerve conduction (Albers et al., 1985). Others, including our own group, found normal sensory potentials despite severe motor abnormalities within the same compound nerve in several patients (Raman and Taori, 1976; van der Meché et al., 1988a).
In *serial nerve conduction studies* initially normal or near normal conduction velocities were found (Peterman et al., 1959; Lambert, 1960; Humphrey, 1964; Kaeser, 1964; Lambert and Mulder, 1964; McQuillen and Gorin, 1969; Bigot and Goulon, 1970; Eisen et al., 1974; Kimura, 1975; McLeod et al., 1976; Raman and Taori, 1976; Hausmanova et al., 1979; Wexler, 1980, 1988; McLeod, 1981). Generally the observed changes were reported to occur seemingly at random; there was no correlation with clinical deficit in most studies. Albers pooled the electrodiagnostic findings, combining observations on 180 patients, who were tested in the second until the 20th week after onset of the disease. Motor conduction velocities peaked at 3 weeks after disease onset and sensory abnormalities 1 week later. In completely recovered patients, normal m-NCVs were found in only 1 of 10 patients after 2 years (Martinez et al., 1977). In contrast McLeod found normal NCVs in most of his patients 6 months to 5 1/2 year after onset (McLeod, 1981).
F-response latencies have been used to detect conduction abnormalities in proximal nerve segments (roots, plexus). In patients with normal m-NCVs the incidence of abnormal F-responses varies considerably: by Kimura (1975 et al., 1978) in 23%, by Lachman (1980) in 18%, by Walsh (1984) in 12%, by Mills (1985) in 24%, by Ropper (1985) in 68%. In his series an abnormal F-response was the exclusive finding in 27%. Albers found in his patients the highest incidence of

abnormal F-responses in the 3rd to 5th week after onset (Kimura et al., 1975; King and Ashby, 1976; Kimura, 1978; Lachman et al., 1980; Walsh et al., 1984; Albers et al., 1985; Mills and Murray, 1985; Ropper et al., 1985). Cornblath (1988) found 46% abnormal F-responses in 210 GBS patients, however m-NCV were not always normal in this group (Cornblath et al., 1988).

Proximal conduction block: using electrical percutanous stimulation of the cervical roots, conduction block in proximal nerve segments was found by Brown (1984,1988) in 7 of 17 patients and by Mills (1985,1986) in 5 out of 17 patients (Brown et al., 1984; Brown, 1988; Mills and Murray, 1985, 1986; van der Meché et al. 1986). One study, using this technique, showed recovery of proximal conduction block during clinical recovery of motor symptoms in 3 GBS patients (Berger et al., 1988). However, these studies should, however, be interpreted with care, as supramaximal stimulation of deeply seated nerve bundles may be difficult, especially in pathological changed fibers (chapter 2.2).

Temporal dispersion and conduction block was first described by Lambert in a serial study in a GBS patient (Lambert, 1960). He used surface disk electrodes to record motor responses. In addition, the implication of increased CMAP duration for detection of abnormal temporal dispersion was stressed by this author. Several authors observed dispersion or complete absence of the evoked CMAP on distal nerve stimulation, albeit by means of the technically less reliable use of needle electrodes (Cerra and Johnson, 1961; Bannister and Sears, 1962; Banerji, 1972; Eisen, 1974). Conduction block was clearly revealed but not commented on in a publication by McQuillen in 1971 (McQuillen, 1971). Since, the incidence of conduction block, as defined by CMAP amplitude reduction over the length of the forearm, has varied from 20% to 60% (Lewis and Sumner, 1982; Brown et al., 1984; Feasby et al., 1985; Olney et al., 1987; Albers and Kelly, 1989; Barohn et al., 1989; Uncini et al., 1991; Lange 1992). Brown et al. defined conduction block as a CMAP amplitude reduction of more then 20% over the length of the forearm, precluded that the CMAP duration does not increase by more than 15% (Brown et al., 1984). In 68.4% of his patients conduction block was detected in at least one nerve within two weeks of disease onset. In 15 of 20 nerves a CMAP reduction of more than 50% was found in this study. Cornblath et al. tested 210 patients electrodiagnostically (50% within 10 days and more than 75% within 15 days after onset of the disease) (Cornblath, 1990; Cornblath et al., 1991). He found in 20% abnormal distal CMAP amplitudes and in 30% abnormal CMAP reduction. In the retrospective study of Albers (1985), 50% of the patients had a low CMAP amplitude on distal stimulation in the first week of the illness, which typically further decreased in the second through the third week (Albers et al., 1985). A model of random conduction block in GBS was proposed by van der Meché and Meulstee (van der Meché and Meulstee, 1988).

Today, no generally accepted electrodiagnostic criteria for conduction block are esthasblished.

3.3 Correlation with clinical disability

Isch (1962) found clinical recovery preceeded m-NCV normalisation, while Bergamini (1966) found a correlation between rate of clinical deterioration and conduction slowing (Isch et al., 1962; Bergamini et al., 1966). Others could not detect a correlation of conduction abnormalities with clinical disability (McQuillen, 1971; McLeod et al., 1976, 1981; Hausmanova et al., 1979; Wexler, 1980). Even normal nerve conduction velocities in peripheral nerves have been found despite clinical disability (Lambert and Mulder, 1964; Bergamini, 1966; Eisen et al., 1974; Raman and Taori, 1976; McLeod et al., 1976, 1981). Several authors have found conduction slowing to be correlated to prolonged time to recover in some of their patients (Eisen, 1974; Humphrey, 1964). In contrast McQuillen (1969) found conduction slowing to be associated with outcome (McQuillen and Gorin, 1969). However, in the group of 7 patients with fast recovery, 6 children, known to have a better a priori outcome, were included. Eisen (1974) and Wexler,(1980) found that sensory nerve conduction may further decrease in the presence of clinical improvement (Eisen et al., 1974; Wexler, 1980). Eisen (1974) and Raman (1976) found that the presence of denervation potentials was associated with increased recovery time (Eisen et al., 1974; Raman and Taori, 1976). Berger showed recovery of proximal conduction block at the time that motor deficit vanished in 3 GBS patients using cervical root stimulation (Berger et al., 1988). We found a correlation between CMAP amplitude after distal stimulation and clinical deficit (van der Meché et al., 1989).

3.4 Diagnosis

Most authors have agreed that electrodiagnostic tests are important to support clinical diagnosis of demyelinative polyneuropathies (Eisen et al., 1974; McLeod, 1981; Kelly, 1983; Takeuchi et al., 1984; Albers et al., 1985; Albers and Kelly, 1989; Cornblath, 1990; Olney et al., 1990; van der Meché et al. 1991; Bromberg, 1992; Unchini, 1993). Several different sets of criteria have been proposed, all with resulting different sensitivity and specificity (Kelly, 1983; Albers et al., 1985; Albers and Kelly, 1989; Cornblath, 1990; Bromberg, 1992). These sets, however, were mainly constructed for and tested in chronic demyelinating polyneuropathies, in which m-NCVs more frequently show severe slowing compared to GBS. Therefore, their sensitivity for the diagnosis of GBS remains to be esthablished.

3.5 Prognosis

In mostly retrospective studies, low CMAP-amplitude after distal stimulation has been found to correlate with poor recovery (Ropper et al., 1986; Gruener et al., 1987; Cornblath et al., 1988; McKahn et al., 1988; Miller et al., 1988; Winer et al., 1988; Meulstee et al., 1991; van der Meché et al., 1992). The presence of denerva-

tion potentials predicted poor outcome in several studies (Brown et al. 1984; Feasby et al., 1986; Gruener et al., 1987; McLeod, 1981; Miller et al., 1988). A similar but weaker predictive power was esthablished for m-NCV (Cornblath et al., 1988). Several authors found that patients with denervation potentials had slower recovery (Eisen et al., 1974; Raman and Taori, 1976; Mcleod, 1981). Others described the association between low CMAP amplitudes with denervation potentials and poor prognosis (Miller et al., 1988; Cornblath et al., 1988).

3.6 Subtypes

Ropper described three predilection sites of conduction deficit: distal, intermediate and proximal (Ropper et al., 1990, 1991). Brown reported distal and proximal conduction failure in addition to conduction failure at usual compression sites to predominate (Brown et al., 1991). Most authors hypothesise that failure of blood nerve barrier plays an important role in the distribution of conduction deficit.
In 1988 we suggested that two patterns of conduction block might be distinguished. In one pattern the sensory system was spared and motor conduction block occurred more or less randomly over the length of the nerve. In the other pattern sensory potentials disappeared and motor conduction block was suggested to be more located in the distal parts of the nerves (van der Meché et al., 1988a, 1988b). In chapter 4 it will be discussed that these patterns in fact appear to be extremes of a continuum.

3.7 Axonal degeneration

Several authors found denervation potentials in GBS with incidences varying from 23%-100% (Eisen et al., 1974 in 23%; Dejesus et al., 1974 in 54%; Raman and Taori, 1976 in 20%; Niewiadomska and Wochnik-Dyjas, 1981 in 30-70%; Brown 1981 in all of 10 patients; Albers 1985, 1986; van der Meché et al., 1988a, 1988b). Denervation potentials were most often found in distal muscles (Raman and Taori, 1976; Niewiadomska and Wochnik-Dyjas, 1981; Brown et al., 1984) and predominantly in lower limb muscles (Brown et al., 1984). In the serial retrospective study of Albers, denervation potentials were most abundant in the 3rd to the 5th week (Albers et al., 1985). DeJesus and Martinez (1977) performed the first quantitative myography and found signs of axonal reinnervation well into the recovery phase (DeJesus, 1974; Martinez et al., 1977).
Mostly, axonal degeneration has been ascribed to be due to demyelination ("bystander phenomenon") (King and Ashby, 1976; Madrid and Wisniewsky, 1976; Asbury and Johnson, 1978; Said et al., 1981; de Waal, 1990), although several authors raised the possibility of a primary axonal lesion (Niewiadomska and Wochnik-Dyjas, 1981; Albers et al., 1985). Feasby was the first author, characterising an acute axonal subtype of GBS defined by widespread axonal degeneration and inexcitable motor nerves along with poor recovery (Feasby et al., 1985, 1993).

Since then, some have argued that the distinction of an axonal subtype was not warranted, because they found signs of demyelination prior to development of severe axonal involvement (van der Meché, 1991a; Triggs et al., 1992; Brown, 1993).

3.8 Summary and conclusion

Since Lambert's original report in 1960 the following basic features have been distillated from electrodiagnostic studies in GBS: early conduction block as reflected by low distal CMAP amplitudes and CMAP reduction with more proximal stimulation and in a later phase of the disease conduction slowing (Cornblath, 1990). Often, however, different electrodiagnostic studies in GBS show conflicting results. This may be due to the variability of the lesions intrinsic to the disease, but likely they are also caused by the very variable timing of the observations in relation to the phase of the disease; many of the earlier studies were done in the plateau or recovery phase and not in the early phase (Kaeser and Lambert, 1962; Pleasure et al., 1968; McQuillen and Gorin, 1969; Eisen, 1974; Martinez et al., 1977; Hausmanova et al., 1979). In several studies, factors associated with poor prognosis were identified. Especially low CMAP amplitudes and denervation potentials were significant predictors of poor outcome; decreased m-NCV was a less reliable predictor of poor outcome.
Generally these studies have shown what electrodiagnostic parameters are to be tested in Guillain-Barré syndrome. Over the recent years CMAP parameters have been more important than the study of nerve conduction velocities.

Chapter four

Electrodiagnostic findings and patterns in the Guillain-Barré syndrome

4.1 Introduction

In the Guillain-Barré syndrome electrodiagnostic evidence for demyelination is regarded as strong diagnostic support (Asbury and Cornblath, 1990). Slowing of conduction has at first been emphasised, but this may appear relatively late in the disease (McLeod, 1981). Later, conduction block and abnormal dispersion of the CMAP between proximal and distal stimulation sites have been discussed (Brown and Feasby, 1984; van der Meché et al., 1988b; Albers and Kelly, 1989; Cornblath, 1990; Feasby, 1992). Low CMAPs after distal stimulation have been shown to have prognostic value, but is not specific for demyelination (Winer, 1985; Cornblath et al., 1988; Albers and Kelly, 1989; Meulstee et al., 1991; van der Meché et al., 1992). In general a substantial variability between patients and between studies has been found. This may in part be due to the timing of the electrodiagnostic studies relative to the phase of the disease. Many studies have been transversal, retrospective or without a standard time schedule. At the other hand, different pathophysiological mechanisms may exist in GBS leading to different electrodiagnostic patterns. We have described such patterns in individual GBS patients, that were either characterised by a pure motor form with random conduction block or by a sensory motor form with predominantly low distal CMAPs and prolonged distal motor latencies (van der Meché et al., 1988a, 1988b).
In the Dutch GBS trial we were able to study longitudinally 135 patients following a fixed time schedule. Three electrodiagnostic studies were longitudinaly performed at entry and one and four weeks later to answer the following questions: 1. How do the abnormalities described above develop during the course of the disease?; 2. What is the optimal timing for electrodiagnostic studies in GBS patients with regard to an optimal yield of abnormalities to use for diagnostic and prognostic purposes?; 3. Is it possible to characterize subgroups of patients with defined electrodiagnostic patterns?

4.2 Patients and methods

147 Patients fulfilling the criteria for acute Guillain-Barré syndrome, were followed for 6 months in the multicentre Dutch Guillain-Barré Trial, which was a randomised trial comparing intravenous immune globulin and plasma exchange treatment (van der Meché et al., 1992). Patients had to be ill for less than two weeks and had to be unable to walk independently to be included in the study. Dependent on the clinical condition, electrodiagnostic testing (EMG) was perfor-

med in warm EMG rooms or intensive care units. Normal reference values were obtained according to the same EMG protocol in a group of 45 healthy volunteers. Using linear regression, we constructed temperature dependent limits of normal for distal motor latencies and nerve conduction velocities.
Ulnar and median motor and sensory nerves were tested, using standardised conventional techniques. The peroneal motor nerve and sural nerve were additionally tested in part of the centers. As a group, these patients were not different from the patients in the centers where the peroneal and sural nerves had not been tested. Motor nerve conduction velocities, distal motor latencies and CMAPs were obtained after distal and proximal stimulation (i.e. wrist and elbow, ankle and knee). Sensory nerve conduction velocities (s-NCV) and CSNAPs were obtained antidromically using recording electrodes on the fifth and second fingers, respectively and for the sural nerve on the foot. Minimal F-response latencies were obtained after 20 stimuli applied distally. F-M latencies were computed by subtracting the distal CMAP latency from the F-response latency.
Utmost care was taken to stimulate nerves supramaximally and to search for the maximal CMAP above the muscle belly with surface disk electrodes. CMAP-amplitudes of the hypothenar, thenar and extensor digitorum brevis muscles were measured as peak-to-peak values as well as duration of the negative phase. CMAP-amplitude reduction is important to diagnose demyelination. In general, a reduction of the CMAP after proximal versus distal stimulation with a higher percentage than in a reference group has been taken as abnormal. 20% Reduction is taken as a limit by several authors (Feasby et al., 1985). Because the error of CMAP measurement is approximately 1 mV, the use of a percentage as the criterion for abnormal amplitude reduction is only reasonable if the CMAP amplitude after distal stimulation (distal CMAP) is not too low. Below 5 mV the error of 1 mV in itself may lead to a CMAP reduction percentage of 20. Therefore, we have taken as evidence for significant amplitude reduction a decrease of the CMAP amplitude beyond the limit of normal for a particular nerve; in the case of a low CMAP (<5 mV) we take a decrease of 1 mV.
To obtain an impression of temporal dispersion, the percentage of increment of the duration of the negative phase of the CMAP was computed.
Myography was performed using concentric needle electrodes in the abductor pollicis brevis, abductor digiti minimi and anterior tibial muscles. At several sites in the muscle, the presence and density of denervation potentials were estimated as follow: 0 = not present; 1 = a few present; 2 = many denervation potentials, but baseline not completely filled; 3 = many denervation potentials and baseline completely filled. Recruitment pattern on maximal voluntary effort (pattern) was also tested and estimated as follow: interference pattern (IP) = normal i.e. full pattern; mixed pattern (MP) = moderately decreased pattern; single pattern (SP) = severly decreased pattern; 0 = no motor unit potentials recognisable. Skin temperature of all stimulation and recording sites as well as muscles were measured.
Electrodiagnostic testing was scheduled within two days after entry, one week later and one month later.

Of all electrodiagnostic variables, median values and their 5 - 95 interpercentile range were computed as well as the average surface skin temperature.
In addition, the percentage of patients with abnormal values according to temperature dependent normal values were computed for variables in each of the three EMGs. Similarly, the percentage of abnormal F-M wave latencies was counted; however, this was only done in nerves with a normal distal m-NCV.
The change of values throughout the three EMGs was computed, only if the difference in skin temperature between consecutive examinations did not exceed 1° Celsius. Formal cluster analysis, using the computer programm SSPS, was performed to search for subgroups.

4.3 Results

Timing of EMG was scheduled according to the time of entry into the trial. At that moment patients were unable to walk independently. At the time of the first EMG, they had been complaining of weakness for an average of 6 days (90% of the patients: 2-15 days) (table 2). Average skin temperature varied from 30.4° - 32.4° Celsius for most nerves (table 3).

Table 2. Duration of weakness (days) at the moment of EMG.

	median	range 5% - 95%
EMG I	6 days	2 - 15 days
EMG II	13 days	9 - 22 days
EMG III	34 days	29 - 49 days

Distal motor latencies and conduction velocities: The means and ranges for all three EMGs are given in table 3. It appears that the average DML and NCV for the group do not change much during the course of the disease. In table 4 the percentages of patients are given, who had an abnormal value. In the first EMG about 80% of the patients had an abnormal DML in the upper limb nerves. About 50% had abnormal m-NCVs and s-NCVs in the first EMG. The sural nerve was involved in about 40%. All these percentages increased somewhat over the period of a month. The percentage of patients with abnormal F-M wave latencies in combination with normal m-NCVs was 8% - 13% in upper limb nerves and 0% in the peroneal nerve. F-responses could not be elicited in 9%, 5% and 23% from median, ulnar and peroneal nerve respectively in the first EMG.
CMAP amplitudes after distal stimulation: Median values were far below lower limit of normal (LLN) in all three EMGs (fig. 6). The percentage of patients with abnormal CMAP amplitudes in the first EMG was 86% and 97% in the upperlimb nerves (table 4) and 75% in the peroneal nerve. The incidence of inexcitable nerves became maximal in the third EMG. It was more frequently observed in the peroneal nerve (17%) compared to upper limb nerves (both 6%) (table 3).

Table 3a. Median and range of conduction velocities in EMG I.

	mean	range	temp	SD	n
DML					
ulnar	3.8 msec.	2.6-6.4	31.6°C	2.2	123
median	5.1 msec.	3.2-11.2	31.9°C	1.9	119
peroneal	5.5 msec.	3.7-9.4	30.4°C	2.1	52
m-NCV					
ulnar	52 m/sec.	34-64	32.2°C	1.7	119
median	47 m/sec.	26-60	32.3°C	1.5	117
peroneal	39 m/sec.	21-53	30.8°C	1.4	51
s-NCV dist.					
ulnar	44 m/sec.	33-60	31.0°C	4.2	73
median	50 m/sec.	30-62	31.6°C	2.3	77
sural	43 m/sec.	33-54	30.4°C	1.9	32
s-NCV prox.					
ulnar	58 m/sec.	45-73	31.8°C	1.8	62
median	57 m/sec.	40-68	32.2°C	1.7	63

Tabel 3b. Median and range of conduction velocities in EMG II.

	mean	range	temp	SD	n
DML					
ulnar	3.9 msec.	2.4-9.5	32.0°C	1.9	118
median	5.7 msec.	3.0-14.2	32.1°C	1.8	118
peroneal	5.4 msec.	3.7-13.3	30.7°C	2.2	45
m-NCV					
ulnar	50 m/sec.	27-63	32.2°C	1.6	116
median	47 m/sec.	25-58	32.4°C	1.6	115
peroneal	37 m/sec.	18-55	31.1°C	1.8	44
s-NCV dist.					
ulnar	44 m/sec.	22-61	31.5°C	3.0	66
median	50 m/sec.	36-62	31.8°C	3.0	66
sural	42 m/sec.	33-52	30.5°C	2.3	24
s-NCV prox.					
ulnar	58 m/sec.	39-71	32.0°C	2.0	56
median	57 m/sec.	29-69	31.0°C	1.7	56

Table 3c. Median and range of conduction velocities in EMG III.

	mean	range	temp	SD	n
DML					
ulnar	4.2 msec.	2.5-11.3	31.1°C	2.2	108
median	6.2 msec.	3.3-16.9	31.4°C	2.0	107
peroneal	7.0 msec.	3.2-15.6	29.5°C	2.1	36
m-NCV					
ulnar	46 m/sec.	19-62	31.7°C	1.9	103
median	45 m/sec.	21-57	32.1°C	1.7	104
peroneal	37 m/sec.	24-48	30.4°C	1.6	34
s-NCV dist.					
ulnar	41 m/sec.	18-56	30.5°C	2.5	71
median	44 m/sec.	23-57	31.0°C	2.5	68
sural	40 m/sec.	14-59	29.4°C	2.2	18
s-NCV prox.					
ulnar	56 m/sec.	42-69	31.0°C	2.0	55
median	56 m/sec.	39-71	32.0°C	1.8	55

CMAP-amplitude reduction with more proximal stimulation compared to distal stimulation: abnormal CMAP-amplitude reduction, defined as more than the upper limit of normal (ULN) but at least 1 mV were found in 32% in ulnar nerve, in 39% in median nerve and in 17% in the peroneal in the first EMG. The incidence of abnormal reduction tended to decrease in later EMGs (table 4).

Dispersion of CMAPs: median values obtained after distal stimulation exceeded the upper limit of normal in all nerves in the second and third EMGs (fig. 6). The CMAP was prolonged in about 50% in the first EMG in all 3 nerves and increased further by about 5 - 15 % in subsequent EMGs. The percentage with an abnormal increment in CMAP-duration with more proximal stimulation, varied from 17% - 39% in all three EMGs in all nerves (table 4). To estimate the diagnostic value of dispersion in addition to the DML and m-NCV we determined the incidence of abnormal dispersion in combination with normal DML or m-NCV. These incidences varied from 15% to 53% and from 0% to 26% respectively (table 5).

CSNAP-amplitudes: Median values of CSNAPs obtained after distal stimulation were below LLN in the ulnar and median nerves in all three EMGs (fig. 6). In the first EMG, the percentage of patients with abnormal values was higher in the upper limb sensory nerves (22%) compared to the sural nerve (10%). This percentage increased by a further 10% during subsequent EMGs in all nerves tested. In addition, the percentage of patients with amplitudes of 0 uV in upper limb sensory nerves in any EMG after distal stimulation varied from 31% to about 39%, whereas in the sural nerve it was 18% to 22% (table 4).

Table 4. Percentage of patients with abnormal findings in EMG I, II and III.

	limit	EMG I	n	EMG II	n	EMG III	n
DML¶							
ulnar		83%	123	86%	119	85%	108
median		79%	121	76%	118	77%	107
peroneal		23%	53	38%	47	54%	37
m-NCV§							
ulnar		45%	119	56%	116	67%	103
median		64%	117	65%	115	67%	104
peroneal		47%	51	48%	44	53%	34
s-NCV dist§							
ulnar		45%	73	52%	66	56%	71
median		39%	77	38%	66	46%	68
sural		28%	32	29%	24	,39%	18
s-NCV prox§							
ulnar		44%	62	43%	56	58%	55
median		48%	63	48%	56	51%	55
F-M lat.¶							
ulnar	30.0 msec.	13% [9%]	64	15% [4%]	68	16% [4%]	73
median	28.6 msec.	8% 5%]	79	4% [6%]	79	12% [4%]	76
peroneal	55.7 msec.	0% [23%]	22	25% [19%]	16	8% [25%]	12
CMAP-amp dist¶							
ulnar	15.5 mV.	97% [1%]	125	91% [6%]	126	88% [6%]	113
median	12.3 mV.	86% [4%]	125	86% [6%]	127	81% [6%]	117
peroneal	6.0 mV.	74% [9%]	58	71% [13%]	55	75% [17%]	47
CMAP-reduction							
ulnar		32%	120	36%	118	33%	104
median		39%	119	29%	119	29%	109
peroneal		17%	52	27%	44	3%	38
CMAP-dur dist¶							
ulnar	8.1 msec.	48%	93	65%	92	53%	81
median	7.2 msec.	49%	87	74%	91	66%	83
peroneal	6.7 msec.	55%	38	60%	30	69%	26
CMAP-dur incr.¶							
ulnar	12%	21%	89	28%	89	39%	76
median	12%	17%	82	34%	90	30%	80
peroneal	19%	38%	37	25%	28	18%	22
CSNAP-amp dist¶							
ulnar	10 uV.	23% [31%]	121	24% [37%]	117	32% [30%]	109
median	10 uV.	22% [33%]	125	25% [39%]	121	29% [34%]	112
sural	5 uV.	10% [18%]	39	5% [17%]	30	22% [22%]	23

Values in square brackets represent the incidence of unelicitable responses not included in the percentage of abnormal values. Sensory nerve conduction velocities were obtained in the hand (s-NCV dist.) and in forearm (s-NCV prox.) segments. CMAP-amp dist. and CMAP-dur dist. indicates the CMAP amplitude and CMAP duration respectively, after distal stimulation. CMAP dur incr. indicates increment of CMAP duration between two stimulation points. ¶ Upper limit of normal and § lower limit of normal according to our laboratory's reference values; in the case of DML and NCV according to temperature dependent limits.

Density of denervation potentials: About 10% of the patients had denervation potentials in the first EMG, usually grade 1 or 2. The incidence and severity reached a maximum in the third EMG (40%-65%) of all patients. Denervation potentials were more frequently present in the anterior tibial muscle (65%) than in the small hand muscles (40%-43%) (table 6).
Recruitment pattern on maximal voluntary contraction: 41%-62% of the patients had no voluntary recruitment pattern (0) or a severely decreased pattern (SP) at the first EMG. These percentages decreased between the second and the third EMGs (table 7).

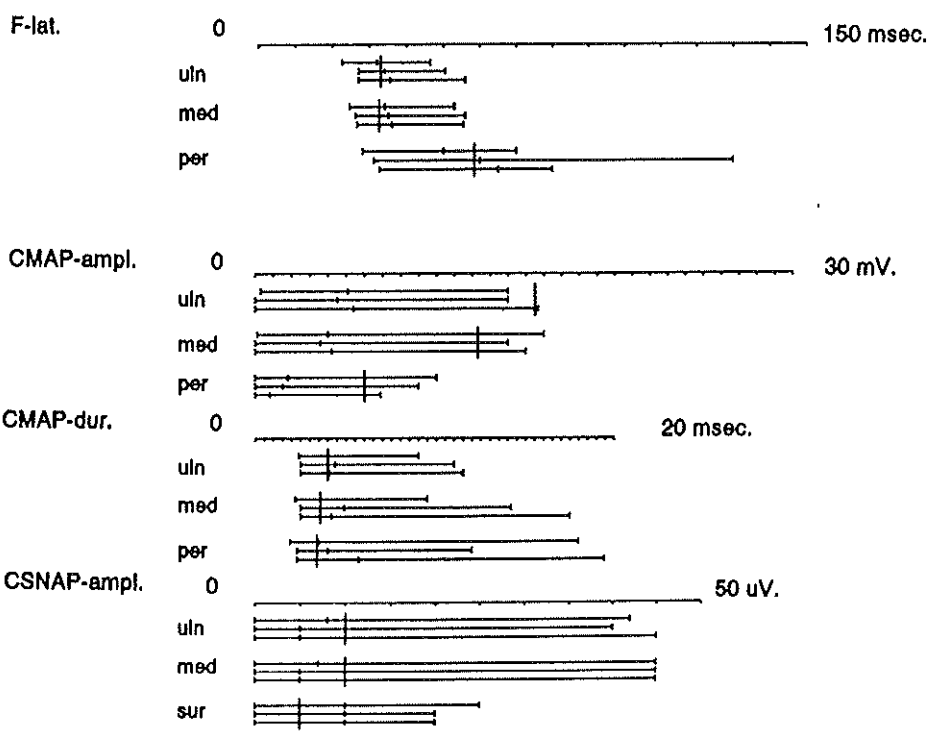


Fig. 6. Median values, 5-th and 95-th percentile ranges of electrodiagnostic findings.
Data obtained in the first, second and third EMG are represented by a bundle of three consecutive bars. Limit values are indicated by one vertical bar per bundle.

Table 5. Incidence of abnormal temporal dispersion if DML or m-NCV are normal.

	EMG I	EMG II	EMG III
	Abnormal dispersion with distal stimulation		
ulnar	29% (21)	29% (17)	19% (16)
median	15% (26)	32% (28)	25% (25)
peroneal	34% (41)	41% (29)	53% (17)
	Abnormal differential dispersion		
ulnar	17% (65)	18% (51)	26% (34)
median	12% (42)	38% (40)	24% (34)
peroneal	26% (27)	4% (23)	0% (16)

Incidence of abnormally long duration of CMAPs with distal stimulation in patients with normal DML (upper part) or abnormally large increase in duration of CMAPs with proximal compared to distal stimulation in patients with normal m-NCV (lower part). The number of patients with normal DML or normal m-NCV are given in parentheses.

Table 6. Percentage of patients with denervation potentials in various muscles.

	EMG I		EMG II		EMG III	
		n		n		n
M. ADV	9%	102	18%	107	40%	98
M. APB	10%	106	18%	109	43%	98
M. TA	9%	54	30%	56	65%	55

Electrodiagnostic subtypes were not easily recognised. In an earlier study, some patients showed more or less random conduction block and sparing of the sensory fibers, while other patients showed low distal CMAPs, prolongued DMLs and disappearing sensory potentials (van der Meché et al., 1992).
In the present study 27 patients (18%) had a pure motor form of GBS both clinically and electrodiagnostically, but conduction block was variably present. Likewise in patients with mixed sensory motor involvement clear conduction block was sometimes present. In order to analyse whether two subgroups exist that merge into each other, or whether the variability of findings is better explained by a continuum, cluster analysis has been performed, including all electrodiagnostic variables. This analysis refuted the hypothesis of two merging subgroups.

Table 7. Percentage of patients with reduced recruitment pattern (absent or single motor unit activity).

	EMG I	n	EMG II	n	EMG III	n
M. ADV	50%	103	42%	106	30%	98
M. APB	41%	106	42%	107	32%	101
M. TA	62%	55	53%	54	47%	53

4.4 Discussion

In the present study, in 90% of the patients, the first EMG was performed within two weeks after onset of the weakness. In all patients subsequent EMGs were made 1 and 4 weeks later. Therefore, the present study can be regarded as the first in which a large cohort of clinically defined GBS patients was tested longitudinally in an early stage of the disease. These patients were selected for the Dutch Guillain-Barré Trial and one of the entry criteria was inability to walk independently more than 10 meters; therefore no conclusions may be drawn for mildly affected individuals. Due to the nature of the disease, patients were tested in climate controlled EMG rooms or intensive care units in the 15 hospitals involved. We have paid particular attention to the problem of temperature control. The average skin temperature varied between 30.4° and 32.4° Celsius. We choosed not to warm patients up for practical reasons. Especially in the intensive care unit it is a cumbersome procedure. In addition it is conceivable that the gradient between skin temperature and nerve temperature varies considerably per patient as it depends on the soft tissue volume between skin and nerve. This is to say that two patients that have acquired the same skin temperature may still have significantly varying nerve temperatures. This method may lead to measuring errors, that are not possible to correct afterwards. Other approaches are to correct the measured values especially the DML and NCV for a deviation of the standard temperature or to apply limits of normal dependent on temperature. We applied both these methods; overall the differences were negligible, although for individual patients differences were observed. We have chosen to present the data with temperature dependent limits of the 45 normal controls to judge abnormalities in GBS patients. This is at present the most reasonable approach for this methodological problem, which is difficult to circumvent completely in clinical studies.

DML and CMAP amplitudes after distal stimulation, were abnormal in more than 80% in the first EMG. Therefore, early in the disease conduction abnormalities in distal segments of motor nerves predominate. In general slowed *motor and sensory NCVs* were present in the first EMG in over 50%. In former studies a large variation has been found in the percentage of patients with abnormal DML and NCVs (24% - 87%)(Lambert and Mulder, 1964; McQuillen, 1971; Eisen et al., 1974;

Raman and Taori, 1976; Martinez-Figuerora et al., 1977; McLeod, 1981; Takeuchi et al., 1984; Walsh et al., 1984; Albers et al., 1985; Ropper et al., 1985; Cornblath et al., 1988; Winer et al., 1988; Ropper, 1992). This may be due to sample size, timing of EMG or selection of nerves. In accordance to others (Albers et al., 1985; Ropper et al., 1991), we found a slight preponderance for abnormalities of motor over sensory NCVs. We also confirmed a relative preservation of sural nerve conduction compared to upper limb sensory nerve conduction. This does not necessarily imply a different pathophysiological process. It may be that sensory nerves in the upper limbs, which in contrast to the sural nerve are mixed with motor fibers, are damaged by a bystander process in addition to the direct injury.

Increased DML and decreased NCV reflect decreased conduction velocity in the fastest fibers in the distal segments of the nerve. Additional information concerning conduction velocity of slower conducting myelinated fibers may be obtained from dispersion of the CMAP. Differential dispersion, an increase of the duration after proximal versus distal stimulation, suggests slowing in part of the fibers between the stimulation points. This has been studied especially in those nerves where DML or NCV were normal. In individual nerves with normal DML and m-NCV, dispersion could still be found in 53%. This suggests that dispersion is an independent and sensitive indicator of abnormal conduction.

F-responses are commonly used for the assessment of conduction in proximal segments (Kimura et al., 1975; Kimura, 1978; Lachman, 1980; Honavar et al., 1991).

The incidence of abnormal or absent *F-responses* in the presence of normal m-NCV in distal nerve segments varied from 0% to 25% in the three tested nerves, comparable to the 18-28% found in several earlier studies (Kimura et al., 1975; Lachman et al., 1980; Mills and Murray, 1985). In another study, however, the incidence was much higher (46%), but F-wave abnormalities were counted in the presence of abnormal m-NCV in the same nerve (Cornblath et al., 1988). Because of the limited additional information by testing F-responses, F-response testing may be restricted to diagnostic investigation in patients with normal NCVs.

Abnormally large *CMAP-amplitude reduction* between distal and proximal stimulation sites, in the absence of an abnormal increase in duration of the CMAP, is a sign of conduction block in, and hence the hallmark of acquired demyelinating polyneuropathies. However, CMAP amplitude reduction can also be caused by temporal dispersion, due to increased phase cancellation. Since temporal dispersion is caused by slowing of conduction and therefore closely related to demyelination, we propose to use only CMAP amplitude reduction as one of the criteria for demyelinating polyneuropathies. Taking our criteria (see Methods) of CMAP decrease, the incidence of abnormal CMAP amplitude reduction at the first EMG was 31%, 37% and 15% for ulnar, median and peroneal nerve respectively. In previous studies, incidences of abnormal CMAP-amplitude reduction have been found to vary from 20%-60% (Lewis et al., 1982; Brown and Feasby, 1984; Cornblath et al., 1988; van der Meché et al., 1988).

Denervation potentials were most abundant in the third EMG. It was present in 40% of small hand muscles in 60% of anterior tibial muscle. This is in agreement

with former studies in which the incidence of denervation potentials varied from 20% to 64%. (Albers, 1985; Brown and Feasby, 1984; Eisen et al., 1974; Raman and Taori, 1976). Since denervation potentials may be found already in the first EMG, it is suggested that at least in part of the patients loss of axonal function may start distally in the terminal motor nerve twigs and hence does not necessarilly forcast general axonal involvement. This would agree with reports that denervation is not necessarily related to poor outcome (Ropper et al., 1990; Meulstee et al., 1991).

The mean parameter values do not change substantially over the three EMG examinations (Table 3). However, in the individual patients, more dramatic changes may be found in the progressive phase of the disease. We suggest that the optimal timing for final electrodiagnostic testing is at the nadir, which corresponds with the timing of our EMG II. This holds thrue both for diagnostic confirmation and to make a contribution in the evaluation of the prognosis. An earlier EMG may be falsely negative for the diagnosis and too optimistic for the prognosis. Later EMGs tend to diverge in a group with more severe changes in slowly improving patients and a group who is already improving. This is reflected by the increase of the measured range of many parameters in EMG III (table 2).

In an earlier report we described two *patterns of conduction failure* in GBS (van der Meché and Meulstee, 1988), that later received support (Brown and Snow, 1991). In one pattern, CMAP amplitudes became lower with progressively proximal stimulation of the nerve with preserved sensory conduction. In the other type low CMAP amplitudes on distal stimulation and proximal stimulation were accompanied by absent sensory conduction. In the present study, these two patterns were not found as two exclusive GBS subgroups. Cluster analysis showed that they most likely represent two extremes of a continuum. Nevertheless, the extremes that may exist in individual patients indicate that different immune mechanisms may play a role. A diversity of immunological and pathological mechanisms has been linked to the clinical and electrophysiological variability (van der Meché et al., 1994).

From this study it is clear that the predominant electrophysiological changes are distal in the nerve and to a lesser extent in intermediate nerve segments. Part of the preponderance of a low distal CMAP, may perhaps be ascribed to the vulnaribility of the transition from myelinated to unmyelinated in the terminal nerve twig and loss of contact between the axon terminal and the muscle receptor due to axonal changes secondary to more proximal demyelination (Madrid and Wisniewsky, 1976; de Waal, 1990). At the other hand it might be explained by the free access of soluble immune mediators to the intramuscular nerve branches, where the blood nerve barrier is absent. Activated T-cells, able to pass the blood nerve barrier, may be responsible for the more limited changes in the intermediate nerve segments (van der Meché and van Doorn, 1994).

Combined electrodiagnostic and immunological studies are necessary to clarify this.

Chapter five

Electrodiagnostic criteria for polyneuropathy and demyelination: application in 135 Guillain-Barré patients

5.1 Introduction

The Guillain-Barré syndrome is a subacute polyradiculoneuropathy causing severe flaccid quadriparesis. The precise aetiology is unknown but immune mechanisms are involved. In the recent past several therapeutic regimes have emerged, all of which help to reduce the duration and severity of the disease as well as the incidence and duration of respirator dependancy. (Guillain-Barré syndrome study group, 1985; French cooperative group, 1992; van der Meché et al., 1992). Therefore, it is of major importance to have a firm diagnosis as early as possible. Clinical diagnostic criteria have in general been shown to be reliable in the recently conducted clinical trials (Asbury and Cornblath, 1990; van der Meché et al., 1991). Electrodiagnostic tests may, however, in some cases be necessary in the differential diagnosis of GBS. Moreover, in cases of clinically defined GBS, electrodiagnostic studies and more specifically nerve conduction studies may show signs of demyelination, and thus further characterise clinically defined GBS as demyelinating GBS. This may, in the future, prove to be of help in the selection of specific treatment modalities. In the present study we constructed two sets of electrodiagnostic criteria, which are based on the findings in patients included in the Dutch Guillain-Barré Study (van der Meché et al., 1992). The first set can be used to prove the existence of a polyneuropathy. The second set was designed to test the presence of electrodiagnostic signs of demyelination. In addition, we tested several, previously published sets of electrodiagnostic criteria constructed for demyelinating polyneuropathies (Albers and Kelly, 1989; Barohn et al., 1989; Asbury and Cornblath, 1990; Bromberg, 1991).

5.2 Patients and methods

Patients tested in this study were all included in the Dutch Guillain-Barré Trial which tested the efficacy of intravenous immune globulin versus plasma exchange in 147 patients (van der Meché et al., 1992). Patients had the disease for less than two weeks and were unable to walk independently. The results of electrodiagnostic tests were not part of the inclusion criteria. Electrodiagnostic tests were scheduled within two days of entry, one week later and one month later.
The methods of electrodiagnostic testing have been discussed in detail elsewhere (van der Meché et al., 1988). In short: motor nerve conduction studies were performed in ulnar and median nerves. Shortest F-response latencies were measured after 20 stimuli. Sensory nerve conduction velocities of ulnar and median nerves were

measured antidromically. Amplitudes and duration of the evoked motor and sensory responses were measured using surface electrodes. Facultatively the peroneal and sural nerves were also tested. Using concentric needle electrodes, small hand muscles and anterior tibial muscles were tested for the presence of denervation potentials and to study recruitment pattern on maximal voluntary effort.
Electrodiagnostic variables used for constructing the sets of criteria were: DML, m-NCV, F-response latency, CMAP amplitude and duration after distal stimulation, ratio of distal versus proximal CMAP-amplitude, ratio of distal versus proximal CMAP-duration, CSNAP amplitude, s-NCV, recruitment pattern and presence of denervation potentials (table 8). Some values were not scored, but these were not particularly confined to a particular clinical state. In 135 patients at least one EMG was performed.

Table 8. Proposed and tested set of electrodiagnostic criteria for polyneuropathy. ULN upperlimit of normal; LLN lower limit of normal.

At least 3 of the following abnormalities should be demonstrated per nerve in at least 2 nerves :

1. DML > ULN;
2. m-NCV < LLN;
3. F-wave latency > ULN if m-NCV is normal;
4. s-NCV < LLN;
5. distal CMAP-amplitude < LLN;
6. abnormal CMAP-amplitude reduction:
   CMAP-amplitude reduction above ULN if distal CMAP > 5 mV CMAP-amplitude reduction of 1 mV if distal CMAP lower then 5 mV;
7. distal CMAP-duration > ULN;
8. increase of CMAP-duration > ULN;
9. distal CSNAP-amplitude < LLN;
10. recruitment pattern 0 or SP;
11. presence of denervation potentials.

An electrodiagnostic variable was defined as abnormal if it fell outside limits of normal, which were based on a population of 45 healthy volunteers. We defined abnormal CMAP-amplitude reduction as being present if the observed CMAP-amplitude decrease exceeded ULN; in cases where the CMAP-amplitude after distal stimulation was lower than 5 mV, we defined abnormal CMAP-amplitude reduction to be present if the difference between distal and proximal stimulation was at least 1 mV. Recruitment pattern was defined as abnormal if no pattern or a single pattern was obtained on maximal voluntary effort.
In order to diagnose polyneuropathy on the basis of electrodiagnostic criteria, at least two different nerves were required to be abnormal. For a nerve to be considered abnormal, at least three electrodiagnostic variables had to be abnormal (table 8). Absent data may bias the findings towards a lower incidence of abnormal EMGs in the patient population as a whole. Therefore nerves in which only four electrodiagnostic variables were tested were excluded, unless 3 or more variables

were abnormal; throughout the Results section the number of nerves tested is indicated. In addition, other numbers of abnormal variables were also applied and the resulting effect on the sensitivity and specificity was tested. The results of the first two EMGs were used to compute the sensitivity of neuropathy criteria, since these are only of relevance for early diagnosis.
In addition to neuropathic criteria in general, the following findings, characteristic for demyelination, were evaluated: severe slowing of conduction, abnormal dispersion and abnormal CMAP-amplitude reduction (van der Meché et al., 1988; Albers and Kelly, 1989; Brown, 1993). We defined signs of demyelination to be present in a peripheral nerve if at least one of the aforementioned criteria was fulfilled; two different levels of abnormality were tested (table 9 set A, set B). The poly-neuropathy was considered to be demyelinating if two or more nerves showed signs of demyelination (table 9). The number of patients with sufficiently number of tested nerves is presented throughout the results section. In addition, we tested the sensitivity of several previously designed sets of criteria for demyelinating polyneuropathy in the same group of patients. Here again, a correction for bias due to absent values was performed and true incidence was calculated as the ratio between sufficiently tested patients and patients with electrodiagnostic abnormalities.

Table 9. Criteria for primary demyelination. ULN upperlimit of normal; LLN lower limit of normal.

SET A Proposed and tested set: 1 of the following abnormalities per nerve in at least 2 nerves should be demonstrated:

1. DML > 150% of ULN ;
2. m-NCV < 70% of LLN ;
3. F-wave latency > 150% of ULN ;
4. Abnormal CMAP-amplitude reduction > ULN.
5. Abnormal distal temporal dispersion: distal CMAP duration > 150% ULN;
6. Abnormal temporal dispersion: distal to proximal CMAP duration ratio > 150% of ULN.

SET B Proposed and tested set: 1 of the following abnormalities in at least 2 nerves should be demonstrated:

1. DML > 300% of ULN ;
2. m-NCV < 60% of LLN ;
3. F-wave latency > 150% of ULN ;
4. Abnormal CMAP-amplitude reduction > ULN.
5. Abnormal distal temporal dispersion: distal CMAP duration > 300% ULN;
6. Abnormal temporal dispersion: distal to proximal CMAP duration ratio > 300% of ULN.

Table 10. Incidence of abnormal nerves related to the required number of abnormal variables within a nerve.

	EMG I				EMG II			
	ulnar	median	peroneal	> one nerve	ulnar	median	peroneal	> one nerve
3 out of 5§	88% (124)	90% (125)	70% (57)	85% (127)	93% (124)	93% (126)	77% (64)	93% (128)
4 out of 5§	71% (124)	78% (125)	39% (57)	64% (127)	81% (123)	85% (126)	20% (55)	78% (127)
5 out of 5§	50% (124)	50% (124)	27% (56)	40% (126)	63% (123)	66% (125)	33% (51)	50% (125)
5 out of 7§	53% (116)	52% (122)	30% (50)	42% (118)	64% (122)	68% (120)	37% (46)	53% (121)

§ The first number gives the required number of abnormal variables, the second the required number of evaluated variables. Between brackets the number of sufficiently tested patients.

5.3 Results

The median duration of weakness was 6, 13 and 28 days, respectively, at the moment of the 3 subsequent EMGs (table 2).

I. At the first EMG most nerves were abnormal : ulnar nerve 88%, median nerve 90% and peroneal nerve 70%. If criteria other than 3 abnormal variables out of at least 5 variables tested were applied, the yield of abnormal nerves was generally lower (table 10). The same trend was observed in the second EMG, but here the incidences were higher. In the 45 normal subjects these percentages were always zero.
The diagnosis of a polyneuropathy, defined as having at least two abnormal nerves was made in 85% after the first EMG and in 93% after the second EMG. Again applying other criteria yielded lower results. None of the normal volunteers had electrodiagnostic signs of polyneuropathy (table 10).

Table 11. Incidence of motor nerves with at least one sign of demyelination.

SET A	normal controls	EMG I	EMG II	EMG III
ulnar nerve	9% (45)	54% (124)	69% (121)	74% (109)
median nerve	7% (45)	72% (120)	75% (130)	68% (130)
peroneal nerve	11% (45)	51% (53)	52% (50)	56% (39)
two or more nerves	0% (45)	60% (124)	66% (124)	72% (109)

SET B	normal controls	EMG I	EMG II	EMG III
ulnar nerve	9% (45)	33% (124)	44% (121)	49% (109)
median nerve	7% (45)	46% (120)	51% (130)	41% (130)
peroneal nerve	9% (45)	38% (53)	38% (50)	15% (39)
two or more nerves	0% (45)	27% (124)	36% (124)	34% (109)

Set A : If one of the following is true DML > 150% of ULN; NCV < 70% of LLN; F-lat > 150% of ULN if m-NCV is within normal limits; abnormal CMAP-amplitude reduction (see methods); temporal dispersion >150% ULN). Between parenthesis the number of sufficiently tested nerves.

Set B : If one of the following is true DML > 300% of ULN; NCV < 60% of LLN; F-lat > 150% of ULN if m-NCV is within normal limits; abnormal CMAP-amplitude reduction(see methods); temporal dispersion > 300% ULN).

II. Evidence for demyelination, as defined by criteria in set A, was seen in 54%, 72% and 51% in the ulnar, median and peroneal nerves, respectively, in the first EMG. In 60%, signs of demyelination were present in at least two nerves simultaneously (table 11). If criteria were more stringent, as in set B, the yield for individual nerves was 33%, 46% and 38%, respectively, and for at least two nerves only 27% (table 11). In subsequent EMGs these incidences increased maximally with an additional 17%. None of 45 healthy volunteers had signs of demyelination in more than one nerve according to the sets A or B.

III. Applying previously published criteria for primary demyelinating polyneuropathies, yielded rather low incidences at the first EMG, varying from 3% to 22%, and at the third EMG, 13% to 46% (table 12).

Table 12. Incidence of demyelination according to previously published sets of criteria.

	EMG I	EMG II	EMG III
Albers and Kelly (1989)	5% (122)	11% (117)	15% (104)
Asbury and Cornblath (1990)	22% (74)	39% (57)	46% (63)
Barohn et al. (1989)	3% (119)	8% (116)	13% (101)

Between parenthesis the number of sufficiently tested nerves.

5.4 Discussion

We designed a set of electrodiagnostic criteria for detection of polyneuropathy and a set for detecting signs characteristic of demyelination, and applied these in 135 patients with clinically defined GBS. This is the first study in which such a large group of patients has been followed prospectively according to a standard EMG protocol. During follow-up, in none of the patients the clinical diagnosis of GBS was falcified; it is assumed, therefore, that in the patients the diagnosis was correct.

The first set for the diagnosis of polyneuropathy per sé was compiled from electrodiagnostic variables available from the test-protocol. Because the normal limits for these variables are based on 95th percentiles, the application of individual variables would have a false positive rate of 5%, by definition. Therefore, the major advantage of requiring a minimal number of three abnormal variables per nerve in several nerves was, that the false positive rate was reduced to zero in all 45 healthy individuals and therefore the specificity was 100%. The sensitivity of this set was tested in two EMGs, performed at the moment of entry (EMG I) and

one week later (EMG II); at an early stage of the disease. The number of variables per nerve, required for a nerve to be scored as abnormal, is chosen rather arbitrarily; however, different combinations all yielded a high incidence of poly-neuropathy. The set which scored best was the one which required three abnormal variables in two different nerves (85% in the first EMG and 93% in the second EMG) (table 10). Ulnar and median nerves contributed slightly more than the peroneal nerve (about 88% , 90% and 70%, respectively, in the first EMG, table 10). No such sets of criteria are as yet not available in the literature for comparison.

Electrodiagnostic criteria, usually applied for the detection of demyelination, are DML, m-NCV, F-lat and CMAP reduction and duration of CMAPs, because these variables are related to nerve conduction slowing and conduction block (Barohn et al., 1989; Albers and Kelly, 1989; van der Meché et al., 1988; Brown and Bolton, 1993; Albers et al., 1985). In the present study, the threshold value, that would discriminate, had to be chosen rather arbitrarily, as has been done by others (Albers and Kelly, 1989; Asbury and Cornblath, 1990; Bromberg, 1991). Nevertheless, the present set A yielded a rather high incidence of signs of demyelination (60%, 66% and 72% in consecutive EMGs) (table 11). Again, ulnar and median nerves contributed most (table 9; Set A). If, in contrast, criteria were made more rigid, sometimes more rigid than proposed by others (Asbury and Cornblath, 1990; Albers and Kelly, 1989) then a lower yield of 27%, 36% and 34% in three consecutive EMGs resulted (table 9; set B) (table 11). The cause of this lower yield lies in the fact, that many GBS patients have (near) normal m-NCVs (Brown and Feasby, 1984; Arnason, 1993) and, as a consequence, will escape detection if the limiting value of NCV is set at a lower value. We think, however, that set A is a very reasonable proposition to use for the detection of demyelination, but a firmer conclusion can only be drawn if this set of criteria has been tested in a group of patients with pure axonal disorders.

If previously designed sets were applied to the GBS patients in the present study, a much lower yield resulted compared to our set A (table 12) (Albers and Kelly, 1989; Barohn et al., 1989; Asbury and Cornblath, 1990; Bromberg, 1991). Only in the second EMG, the criteria proposed by Asbury and Cornblath led to an incidence comparable to our rigid set B (39%). These sets of criteria may therefore be too strict for application in GBS. This may be explained by the fact that these sets were designed for chronic demyelinating neuropathies. In this group of patients, presumably due to the long duration, demyelinating characteristics are often far more pronounced. Our study shows that criteria derived from CIDP are not sufficiently sensitive. The electrodiagnostic criteria for demyelination as suggested in this work should idealy be verified by histological studies; this is of course not feasable in a large group of GBS patients.

Several studies, have revealed the demyelinating nature of nerve pathology in GBS (Asbury et al., 1969; Saida et al., 1979; Sumner, 1981; Brown and Bolton, 1993). Feasby et al. (Feasby et al., 1985) were able to relate conduction block to pathological demyelination in nerve biopsies. Also, experimentally induced conduction block -whether mechanically (Denny-Brown and Brenner, 1944a) or immunologically (McDonald, 1963a) is associated with demyelination. These studies suggest,

that significant demyelination will be revealed by conduction block and conduction slowing. However, in a number of nerves these electrodiagnostic signs of demyelination are not found, despite the fact, that demyelination is suspected on the basis of clinical observations. This may occur where lesions are patchy along the nerve outside the segment which can be tested in routine studies. Furthermore, conduction block in the thinner segment of motor fibers may be difficult to detect, as long as a small number of large alpha motor units with thick axons - the principal constituents of the CMAP - are free from demyelination. This has been demonstrated by morphological and physiological studies (Feasby et al., 1985; Brown and Bolton, 1993). Another reason why patients with demyelination may pass undetected using the proposed criteria, is that many GBS patients have a very low distal CMAP-amplitude (van der Meché et al., 1988). As other causes, like axonal degeneration or motor end plate dysfunction cannot be discriminated from distal demyelination, low CMAP amplitudes cannot be applied as a criterion of primary demyelination. Therefore, the patients with predominant distal demyelination, will escape detection and may, in any set, cause a serious underestimation of the incidence of demyelination.

In conclusion: in the 135 GBS patients studied, the proposed set of criteria for polyneuropathy had a sensitivity of 85% and a specificity of 100%. The polyneuropathy was demyelinating in 72% or 36%, respectively, using two sets of criteria for demyelination. The less rigid set is proposed as the more reasonable, but should be tested in other categories of demyelinating and pure axonal neuropathies.

Chapter six

Prognostic value of electrodiagnostic testing in the Dutch Guillain-Barre trial

6.1 Introduction

The pathophysiological hallmark of the Guillain-Barré syndrome is demyelination in peripheral nerves, often followed by secondary axonal degeneration (Arnason, 1993; Asbury et al., 1969; Asbury, 1978b; Madrid and Wisniewsky, 1976; Said et al., 1981). Demyelination causes conduction block resulting in clinical deficit, usually severe quadriparesis, sensory loss and a need for artificial respiration in about 20% of the patients. Electrophysiologically demyelination is reflected by lower amplitudes of evoked motor responses with conduction block and slowed conduction (Brown et al., 1981; McLeod et al., 1981; Brown and Feasby, 1984; Albers et al., 1985; Kimura et al., 1988; van der Meché et al., 1988). Several studies have indicated that low CMAPs are associated with a poor clinical outcome (Gruener et al., 1987; Cornblath et al., 1988; McKahn et al., 1988; Miller et al., 1988; Winer et al., 1988). In these reports electrodiagnostic studies were not always performed at similar stages of the disease. In the Dutch Guillain-Barré trial, comparing the effect of IgIv and PE in 147 Guillain-Barré patients (van der Meché et al., 1992), 3 EMG's were planned: at entry, at one week and 4 weeks after entry into the trial. In this report we studied the predictive value of the electrodiagnostic findings for clinical recovery.

6.2 Patients and methods

147 Patients fulfilling the criteria of GBS (Asbury et al., 1981) were followed for 6 months in the Dutch Guillain-Barré Trial, which was a randomised trial comparing IgIv and PE. In order to enter the study, patients had to be ill for less than two weeks and had to be unable to walk independently. Further details and results of this trial are described elsewhere (van der Meché et al., 1992).
Outcome criteria discussed in this paper are ability to walk independently 8 weeks and 6 months after entry into the trial. These moments were chosen for their clinical relevance in the prognostic calculation. At 8 weeks patients can be divided into two groups of almost equal seize: a fast recovering group, able to walk independently and a slow recovering group, not yet able to walk. The group that is unable to walk independently at 6 months is the group that may be left with considerable deficit. An additional outcome criterion that will be discussed is how much time is needed to be able to walk independently again.

Electrodiagnostic testing was performed by experienced clinical neurophysiologists, all members of the Dutch Guillain-Barré Study Group in temperature controlled rooms, using standardised conventional techniques.

Ulnar and median motor and sensory nerves were tested and the peroneal motor nerve was facultatively tested. Motor nerve conduction velocities, distal motor latencies and CMAPs were obtained after distal and proximal stimulation (i.e. wrist and elbow, ankle and knee). Nerve conduction velocities were corrected for temperature effects (DeJesus et al., 1973; Geerlings and Mechelse, 1985). Minimal F-response latency was determined after 20 stimuli applied distally. Utmost care was taken to stimulate nerves supramaximally and to search for the maximal CMAP above the muscle belly with surface disk electrodes in the tendon-belly montage. CMAP-amplitudes of the hypothenar, thenar and extensor digitorum brevis muscles were measured peak to peak, as well as the duration of the negative phase. Myography was performed using concentric needle electrodes in abductor pollicis brevis (M. APB), abductor digiti quinti (M. ADV) and anterior tibial muscles (M. TA). The presence and density of positive sharp waves and fibrillation potentials (denervation potentials) were estimated as follows: 0 = not present; 1 = a few present; 2 = many denervation potentials, but baseline not completely filled ; 3 = many denervation potentials and baseline completely filled. Recruitment pattern on maximal voluntary effort was also tested and estimated as follows : interference pattern (IP) = normal i.e. full pattern; mixed pattern (MP) = moderate decreased pattern ; single pattern (SP) = severe decreased pattern ; 0 = no motor unit potentials recognisable.
Electrodiagnostic testing was scheduled within two days after entry into the trial, at one week and one month after entry. The results of the second EMG are emphasised here to study prognostic value because the majority of patients were in their nadir at this point, whereas at entry patients were in various stages of progression. Data collected from the first and third EMG were used to study diagnostic criteria and axonal degeneration, respectively; the results will be published separately.
We studied correlations between clinical outcome criteria and electrodiagnostic parameters that consisted of continuous variables (CMAP-amplitudes, distal / proximal ratio of CMAP-amplitudes (CMAP-ratio), difference between CMAP amplitude after distal and proximal stimulation (CMAP-difference), distal motor latency, motor nerve conduction velocities). In contrast, the recruitment pattern was dichotomised into groups with grade 0 or SP and grade MP or IP. Also, density of denervation potentials for individual muscles was dichotomised into groups with grade 0 or 1 and grade 2 or 3. A single general variable for the presence of denervation activity was determined for the three muscles studied. If no denervation was ever found in any muscle, we used to term "absent"; if denervation, scored at grade 2 or 3, was found in more than one muscle, we called it "abundant", and all the findings in between were categorised as "moderate".
The data obtained one week after entry were used to develop a prognostic model. All electrodiagnostic data were dichotomised according to the observed statistical median for reasons of clinical applicability. Differences in proportions between

groups were tested with the chi-square test. With the variables that yielded significant results in univariate analysis, a multivariate analysis was performed to see which set of variables obtained were predictive of ability to walk independently 8 weeks and 6 months after entry.

6.3 Results

6.3.1 Efficacy of follow-up schedule

The mean time interval from entry to the three EMGs was in accordance with the schedule of the trial protocol (table 13). The number of missing data are not particularly confined to one functional grade in any of the three EMG's. As a group, patients in whom a second EMG was not performed, were not different from the group of tested patients. Median time-interval from onset of the weakness until the second EMG was 13 days (inter 5% - 95% percentile range: 9 to 22 days). Most of the patients (87%) were at the nadir of their disease at that time.

Table 13. Time of EMG and number of studies compared to the protocol in 147 patients.

	DAYS AFTER ENTRY *scheduled*	*observed*		NUMBER OF PATIENTS STUDIED		
EMG		median	range*	ulnar	median	ant.tib.
first EMG		1		125	124	56
second EMG	6-8	8	6-12	125	127	55
third EMG	26-30	29	24-40	113	117	47

* Inter 5%-95% percentile range.

6.3.2 Correlation of electrodiagnostic findings with clinical recovery

In general, group average *CMAP-amplitudes* obtained with distal stimulation as well as with proximal stimulation of the ulnar nerve, were significantly higher if patients could walk independently 8 weeks and 6 months after entry, compared to patients unable to walk, although substantial overlap did occur (fig. 7). This was the case for all consecutive EMGs. Similar results were found in other motor nerves again in all EMGs ($p = 0.0001$ for both median nerve and for peroneal nerve in the second and third EMG). CMAP-amplitudes obtained with distal stimulation showed a significant negative correlation with time needed to walk independently (Spearman-Rank). Moreover, in all three tested nerves, the strongest correlation was always found in the third EMG (table 14). If CMAP-amplitudes

obtained in individual patients were summed no stronger correlations were obtained. Seven patients showed absent CMAPs after distal stimulation of the ulnar nerve in the second EMG. None of them was able to walk independently 2 months after entry and only 2 patients 6 months after entry.

Table 14. Correlation of time until independent locomotion and CMAP amplitudes (Spearman).

	M. ADV		M.APB		M.EDB	
EMG	rho	p	rho	p	rho	p
first EMG	-.28	0.0016	-.15	0.095	-.18	0.17
second EMG	-.45	< 0.0001	-.41	< 0.0001	-.46	0.0004
third EMG	-.56	< 0.0001	-.50	< 0.0001	-.70	< 0.0001

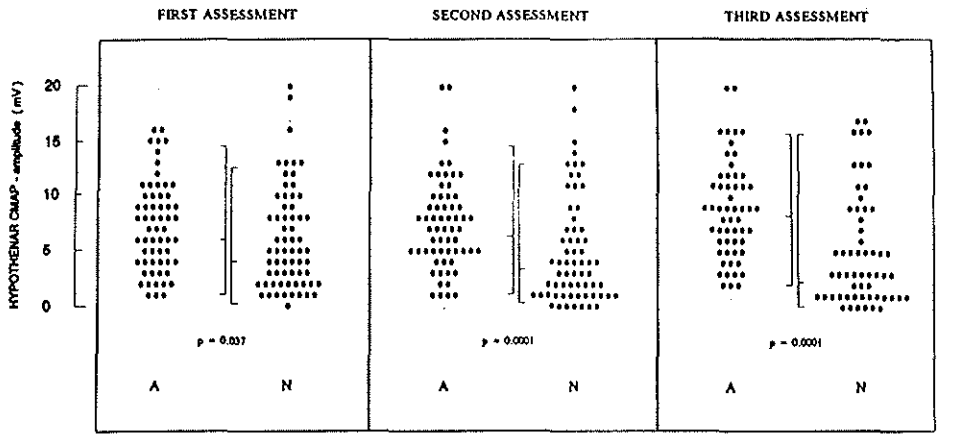
M. ADV abductor digiti minimi muscle; M. APB abductor pollicis brevis muscle; M. EDB extensor digitorum brevis muscle. Rho = correlation coefficient (Spearman).

Decreased ratios of CMAP-amplitudes and absolute differences between CMAPs obtained with proximal and distal stimulation indicate demyelination between the stimulation sites. However, such ratios or differences did not correlate with any outcome measure in any EMG.

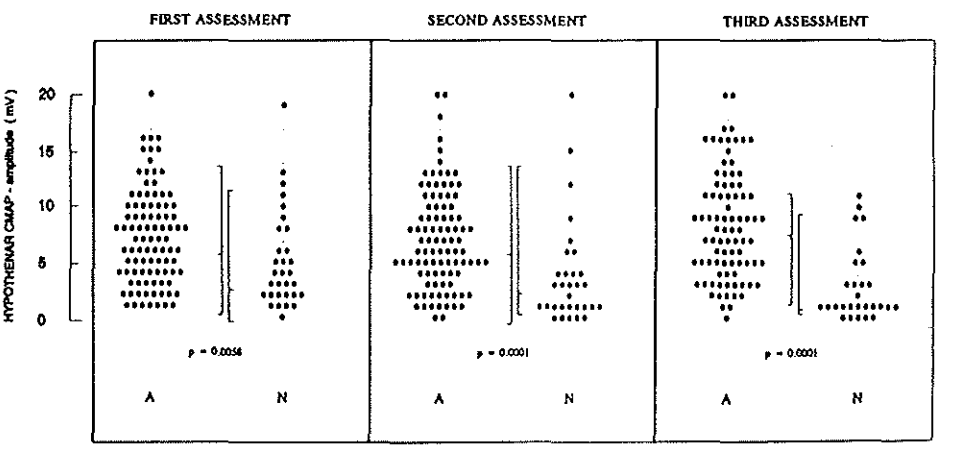
Average *distal motor latencies or minimal F-response latencies* of the three nerves obtained in any of three EMGs did not differ significantly between the outcome-groups. The average *motor conduction velocities* in the forearm segments of ulnar and median nerves were significantly lower only in the second ($p < 0.05$) and in the third EMG ($p < 0.005$) in the groups unable to walk independently at 8 weeks. However, these results were not found for independent locomotion at 6 months.

Recruitment pattern on maximal voluntary effort showed a positive correlation with outcome 8 weeks and 6 months after entry, especially in the second and third EMGs. Time needed to walk independently was significantly shorter if the recruitment pattern was better (table 15).

In most of the patients in whom *denervation activity* developed, the density of denervation potentials was maximal in the third EMG. If denervation potentials were always absent in any muscle there was a 93% chance that patients were able to walk independently 6 months after randomisation (Chi square $p < 0.001$). If abundant denervation activity was present (denervation activity grade 2 or 3 according to the semiquantitative score in at least two muscles in any EMG), there was only a 47% chance of walking independently 6 months after randomisation (Chi square $p < 0.001$). Furthermore, significantly more time was needed to achieve independent locomotion than in the group without denervation activity (table 16).



INDEPENDENT LOCOMOTION 8 WEEKS AFTER ENTRY



INDEPENDENT LOCOMOTION 6 MONTHS AFTER ENTRY

Fig. 7. CMAP amplitudes of hypothenar muscle after distal stimulation of the ulnar nerve in all three EMGs in patients able (A) or unable (N) to walk independently 8 weeks (upper figure) and 6 months (lower figure) after entry, respectively. Bars indicate median value and inter 5% to 95% percentile ranges of CMAP-amplitudes and significance level of difference between outcome groups at each EMG (Mann-Whitney test).

Table 15. Proportion of patients able to walk independently related to recruitment pattern in M. ADV.

	% with independent locomotion at:		Days until independent locomotion:		
Pattern	8 weeks	6 months	mean	SD	number
IP	88%	100%	34	49	8
MP	66%	87%	57	55	53
SP	42%	84%	92	60	31
0	7%	21%	166	39	14
p-value	0.00	0.00	0.00		

Proportion of patients able to walk independently 8 weeks and 6 months after entry and the number of days needed to reach this stage related to recruitment pattern on maximal voluntary effort in M. ADV obtained at the second EMG (see methods).

Table 16. Proportion of patients being able to walk independently related to the general score of density of denervation potentials.

	% with independent locomotion at:		days until independent locomotion:		
density	8 weeks	6 months	mean	SD	number
absent	70%	93%	55	56	43
moderate	40%	72%	97	64	40
abundant	23%	47%	126	67	30
p-value	0.001	0.001	0.001		113

Proportion of patients being able to walk independently 8 weeks and 6 months after entry and the number of days needed to reach this stage related to the general score of density of denervation potentials as defined from all three EMG's (see methods).

6.3.3 Multivariate analysis of prognostic factors

As a preparation for multivariate analysis, univariate analysis was performed using dichotomised values of electrodiagnostic data obtained one week after entry (second EMG). Most of the patients (87%) were at the nadir of the disease at that time. The CMAP-amplitudes obtained after distal and proximal stimulation of ulnar and median nerves and recruitment pattern in all three tested muscles again

proved to be significant predictors for outcome 8 weeks and 6 months after entry. In addition, m-NCV and DML of ulnar and median nerves now appeared to be weak but significant predictors for outcome at 8 weeks only (table 17).

Table 17. Univariate analysis of electrodiagnostic tests of the second EMG in relation to the ability of independent locomotion at 8 weeks.

factor	ceasura	improved	not improved	dif*	p-value
Hypothenar CMAP distal stimulation	< 4 mV	13 (25%)	39	43%	0.000
	> = 4 mV	50 (68%)	24		
Hypothenar CMAP proximal stimulation	< 4 mV	24 (39%)	37	28%	0.003
	> = 4 mV	38 (67%)	19		
DML ulnar nerve	> = 4 mSec	17 (41%)	24	20%	0.042
	< 4 mSec	47 (61%)	30		
Motor NCV forearm ulnar nerve	< 60 m/sec	33 (47%)	37	21%	0.045
	>= 60 m/sec	31 (66%)	16		
Motor NCV upperarm ulnar nerve	< 50 m/sec	12 (43%)	16	24%	0.049
	> = 50 m/sec	28 (67%)	14		
Recruitment pattern M. ADV	0 or SP	14 (31%)	31	39%	0.000
	MP or IP	43 (70%)	18		
Thenar CMAP distal stimulation	< 4 mV	25 (39%)	39	23%	0.010
	> = 4 mV	39 (62%)	24		
Thenar CMAP proximal stimulation	< 3 mV	23 (40%)	34	24%	0.009
	> = 3 mV	41 (64%)	23		
Recruitment pattern M. APB	0 or SP	15 (33%)	30	38%	0.000
	MP or IP	44 (71%)	18		
Recruitment pattern M. TA	0 or SP	9 (31%)	20	33%	0.015
	MP or IP	16 (64%)	9		

* improvement percentage for second category minus improvement percentage for first category.

Multivariate analysis did not select a restricted number of variables important to predict independent locomotion at 6 months. However it yielded two factors which contributed independently to the outcome of independent locomotion at 8 weeks after entry : hypothenar CMAP-amplitude after distal stimulation and recruitment pattern of the abductor digiti minimi muscle (table 18). These results were independent of the kind of therapy used (i.e. Ivlg or PE). Age appearde to have a weak effect on both outcome measures. These two parameters may be used to predict outcome in individual patients. If at the nadir of the disease the CMAP amplitude

is below 4 mV and the pattern is worse than MP, the chance for independent walking 8 weeks after entry is 20%. If, on the contrary, CMAP amplitude exceeds 4 mV and the pattern is better than MP, this chance is 78% (table 19).

Table 18. Multivariate analysis of electrodiagnostic tests of the second EMG in relation to the ability of independent locomotion at 8 weeks.

Factor	Logistic coef.	SE	p-value
Hypothenar distal CMAP	1.53	0.47	0.002
Recruitment pattern M. ADV	1.11	0.47	0.002

Table 19. Predictive value of Ulnar ADV distal CMAP and recruitment pattern of ADV (2-nd EMG).

Ulnar ADV distal CMAP	recruitment pattern of ADV	chance for independent walking at 8 weeks
< 4 mV	< mp	20%
< 4 mV	> = mp	43%
> = 4 mV	< mp	53%
> = 4 mV	> = mp	78%

The chance for independent locomotion at 8 weeks is given by the formula:
p = 1/(1+exp (- (-1.39 + 1.53*a + 1.11*b))); a = 0 if CMAP < 4 mV, else a = 1;
b = 0 if recruitment pattern is worse then mp, else b = 1.

6.4 Discussion

When comparing the EMG at entry, at one week and at four weeks, the second EMG is considered to be the most valuable for prognostic asessment. On the one hand, the results obtained in the second EMG correlated better with outcome compared to the first EMG. This can be explained by the fact that at that moment, most of the patients (87%) were at the nadir of the disease. At the other hand, compared to the timing of the third EMG, the second EMG was still sufficiently early to make a prognostic evaluation useful (median time 13 days). Our first conclusion is, therefore, that prognostic evaluation using electrodiagnostic means can best be done at the early nadir of the disease.
Abnormally low *CMAP amplitudes*, obtained during the nadir, with distal as well proximal stimulation are associated with a poor outcome. These findings are in

accordance with previous prospective studies (Ropper et al., 1986; Gruener et al., 1987; Cornblath et al., 1988). This correlation is, however, weak. The variation in distal ulnar CMAP at the nadir explains only 20% (i.e. rho square) of the variation in time until independent locomotion. From the scatter plot (fig. 7), it is also obvious that in individual patients, low CMAP amplitudes are often not associated with slow recovery. This can also be inferred from comparable plots in other reports (Gruener et al., 1987; Miller et al., 1988). This wide variation may be explained by several factors. If low CMAP amplitudes are caused by distal demyelination, as might occur in a subgroup of Guillain-Barré patients, fast recovery is more likely to occur than in cases where low amplitudes are caused by axonal degeneration (van der Meché et al., 1988, 1991). In addition, axonal damage may be confined to terminal motor twigs (Asbury et al., 1969; de Waal, 1990). In such cases, fast recovery may be expected in contrast to cases in whom the entire axon is damaged. Unfortunately, these causes of low CMAP amplitudes cannot be separated by conventional electrodiagnostic testing. Moreover, falsely low CMAP-amplitudes may be found, due to incorrectly placed electrodes or submaximal stimulation of less excitable nerves. This was, however, anticipated and avoided in the present study by means of a rigid protocol. On the other hand, if high CMAP-amplitudes with distal stimulation are found, technical errors are less likely. However, patients with high CMAP-amplitudes at the nadir, may still recover slowly (fig. 7). Possible explanations are the variability in distribution of weakness over proximal and distal muscles, and the occurrence of more secondary axonal degeneration in the lower compared to the upper limbs. Moreover, it is difficult to judge in individual patients the extent to which the CMAP has decreased. Hypothenar CMAP amplitudes can be as high as 30 mV in healthy individuals; a dramatic fall in amplitude of 25 mV, would still leave a relatively high amplitude of 5 mV. We are, therefore, inclined to be cautious about the short-cut that a hypothenar CMAP-amplitude after distal stimulation bears a simple relationship to prognosis in an individual patient. Absent CMAP-amplitudes after distal stimulation were associated with poor recovery and probably indicates more extensive degeneration of the axons. In such cases recovery will take longer (Triggs et al., 1992; van der Meché et al., 1988, 1991).

Evidence for axonal degeneration as indicated by *denervation potentials* has been associated with a grave prognosis (McLeod, 1981; Brown and Feasby, 1984; Feasby et al., 1986; Gruener et al., 1987; Miller et al., 1988; van der Meché et al., 1991). In our study, however, we found that the presence of abundant denervation potentials is not always associated with a poor prognosis, as reported previously (Ropper et al., 1986; Ropper et al., 1990). First of all this may be caused by the fact that the number of damaged axons is not necessarily reflected by the density of denervation potentials. For instance, density of denervation potentials may show fluctuations according to temperature. Secondly, if axonal degeneration is confined to terminal motor twigs, recovery is likely to be much faster compared to degeneration of the entire axon.

In the present study, *recruitment pattern on maximal voluntary contraction* obtained early in the course of the disease was found to have a significant predictive

value. This variable reflects general nerve fuction. It would be altered by axonal degeneration as well as by conduction block anywhere along the nerve. This test particularly contributes to the assessment of proximally located nerve segments, which can hardly be tested by the use of the CMAP-amplitude as a parameter. Moreover, the recruitment pattern is not influenced by the effects of large variation in individual normal values, as is the CMAP amplitude.

The CMAP-ratio had no predictive value and this is in agreement with other studies (Cornblath et al., 1988). The ratio between proximal and distal CMAP-amplitudes is an important physiological measure as it reflects conduction block. Since conduction block can be quickly restored, one might expect that a lower ratio indicates a good potential for recovery. That this is not true, may be explained by the fact that the ratio is independent of the absolute amplitude. For instance: an amplitude of 5 mV and 10 mV after proximal and distal stimulation, respectively, will result in a CMAP-ratio of 0.5; but amplitudes of 0.5 mV and 1 mV, respectively, give the same ratio, which evidently has different implications (van der Meché et al., 1985). Furthermore, the problem with the CMAP ratio is, that it not exclusively reflects conduction block, but is influenced also by abnormal dispersion. It is very likely, that abnormal dispersion, like m-NCV (see below) is only very weakly related to outcome. (Sumner, 1981, 1992; Olney et al., 1987; Kimura et al., 1988; van der Meché et al., 1988; Rhee et al., 1990). Absolute differences in CMAP amplitudes between distal and proximal stimulation sites, however, did neither have prognostic value.

We found only a weak correlation between *motor-NCV* in forearm nerve segments and outcome. Several previous studies showed conflicting results (see 13 for review). In many severely paretic GBS patients, a normal NCV may be found in the acute phase (Brown and Feasby, 1984; Albers et al., 1985; Ropper et al., 1986), whereas conduction slowing often tends to occur later, possibly as a result of de- and remyelination.

Similar arguments account for the limited value of *F-response latencies* with regard to outcome prediction. Only a very few intact axons can preserve the presence of normal F-responses.

The prognostic value of distal CMAP amplitudes was reduced when adding other prognostic factors in multivariate analysis, like age, duration of illness, artificial ventilation, fuctional score at entry, presence of campylobacter infection and GM1 antibodies (van der Meché et al., 1991). This indicates, that the CMAP is just one of the parameters that reflects severity of weakness.

6.5 Conclusion

For prognostic evaluation in GBS, needle electromygraphy and nerve conduction studies may best be performed as soon as the nadir has been reached. Recruitment pattern on maximal voluntary effort and hypothenar CMAP amplitudes after distal stimulation are the best singular predictors of outcome.

Chapter seven

Axonal degeneration in Guillain-Barré syndrome

7.1 Introduction

The diagnosis of the Guillain-Barré syndrome is made on the basis of generally accepted criteria, the most important being progressive symmetrical paresis and decrease of myotatic reflexes (Asbury, 1981). Demyelination resulting in conduction failure is the cause of the paresis (Arnason, 1993). In later stages of the disease, however, axonal degeneration may be observed in some patiënts. In general, it has been suggested that axonal degeneration is a bystander effect of demyelination in which the axon is the innocent victim of a fulminant attack on its myelin (Madrid and Wisniewsky, 1976; Said et al., 1981; Arnason, 1993). On the other hand, a primary axonal form of GBS has recently been proposed (Albers et al., 1985; Feasby et al., 1986). Conduction block is the physiological hallmark of demyelination. If demyelination is followed by severe axonal degeneration evidence for conduction block should be followed by very low or absent CMAPs and denervation potentials in serial EMG studies. However, the description of such longitudinal EMG studies in individual patients are lacking. In the present report we describe eight patients who developed clinical and EMG evidence of axonal degeneration.

7.2 Patients and methods

Between July 1985 and the end of 1987, 42 GBS-patiënts, both primary and secondary referrals, were seen in our department. Eight patients fulfilled the following criteria for severe axonal degeneration: 1) the presence of denervation potentials; 2) at least one inexcitable nerve and 3) slow clinical recovery (table 20). Patiënts 2, 4-6, 8 and 9 took part in the Dutch multicentre trial comparing high dose intravenous immune globulin (IgIv, Gammagard^{R}-Baxter, Hyland division) with plasma exchange, which explains the different specific treatment modalities in table 20 (Kleyweg et al., 1988). The physiological techniques were similar to those previously published (van der Meché et al., 1988). In all patients median, ulnar and peroneal nerves were investigated at least on admission, and one week and one month later. Stimulus parameters were increased until maximal responses were obtained. Motor fibers were studied by recording with surface electrodes from m. abductor pollicis brevis (APB), m. abductor digiti quinti (ADV), m. tibialis anterior (TA) and m. extensor digitorum brevis (EDB); sensory fibers by recording antidromically from the second and fifth fingers respectively. The latencies and the peak/peak amplitudes of both the sensory nerve action potentials (CSNAP) and the CMAPs were measured. The duration of the negative phase of the CMAP was measured to study differential dispersion. For APB and ADV differential dispersi-

Table 20. Clinical characteristics

Patient	1	2	3	4	5	6	7	8
Age	66	74	72	30	56	45	51	46
Sex	M	M	M	M	M	M	M	M
Days until nadir	5	5	9	11	8	9	5	5
Nadir	Quadriplegic	Quadriplegic	Quadriplegic	Quadriplegic	Almost quadriplegic*	Quadriplegic	Quadriplegic	Almost Quadriplegic*
Period on respirator	0	6 months	3 months	3.5 months	1.5 months	7 months	7 months	0
Function after 6 months	walks with support	Deceased	Chair-bound	Bedridden	Chair-bound	On respirator	On respirator	Walks with support
Specific treatment	IgIv	PE	PE	PE	None	PE	None	IgIv

* Some muscles grade 1 or 2 (MRC)

on was defined as an increase in duration of the negative peak by more than 8%, when stimulation was carried out at the elbow rather than at the wrist (Brown and Feasby, 1984). "Length-dependent CMAP reduction" was defined as a more than 10% decrease in the peak-peak amplitude when proximal was compared with distal stimulation. In the absence of differential dispersion this can be ascribed to conduction block (Brown and Feasby, 1984; Kimura et al., 1986).
For needle myography the following semi-quantitative scoring system was used to describe the presence of fibrillation potentials and positive sharp waves: 0:not present; +:present; ++ many denervation potentials but baseline not filled; +++: baseline completely filled.

7.3 Results

All 8 patiënts were male; their ages ranged from 30 to 72 years (table 20).
All showed denervation potentials and low CMAPs or inexcitable nerves at some stage of the disease (table 21). They could, however, be divided into two groups on the basis of the findings in the first physiological examination. Patiënts 1-5 showed clear evidence of "length-dependent CMAP reduction" and patiënts 6-8 already had low CMAPs in the first study.

Patients 1-5. In the first study all these patients showed considerable length-dependent CMAP and amplitude reduction, i.e. the CMAP decreases with more proximal stimulation. The lack of differential dispersion tends to indicate conduction block along the length of the nerve. At the nadir, however, many of the nerves became inexcitable or showed very low CMAPs without length-dependent amplitude reduction (table 21). Two patients are presented in more detail.

Patient 1 demonstrates the general pattern. In the first study (fig. 8a) he showed conduction block; at this time he had already become quadriplegic. No further clinical deterioration occurred until the next study (fig. 8b). At that time, however, the ulnar nerve had become inexcitable and the median and peroneal nerve showed extremely low amplitudes without length-dependent amplitude reduction (table 21); at the same time abundant denervation potentials became apparent. Recovery was slow and incomplete over a period of 18 months. In this patiënt the sensory system was normal both clinically and physiologically throughout the course of the disease (table 21).
Patient 5 showed conduction block followed by severe axonal degeneration in only some of his muscles, especially those of his right leg. Initially motor deficit was symmetrical but during improvement the right leg lagged behind and this resulted in a prolonged rehabilitation period. The clinical discrepancy was reflected in the discrepancy between the CMAPs of APB and EDB or TA, respectively. Denervation potentials were also abundant in the right leg in contrast to APB. This patient demonstrates that the length-dependent amplitude reduction present in several nerves can be followed by severe axonal degeneration in only some of them.

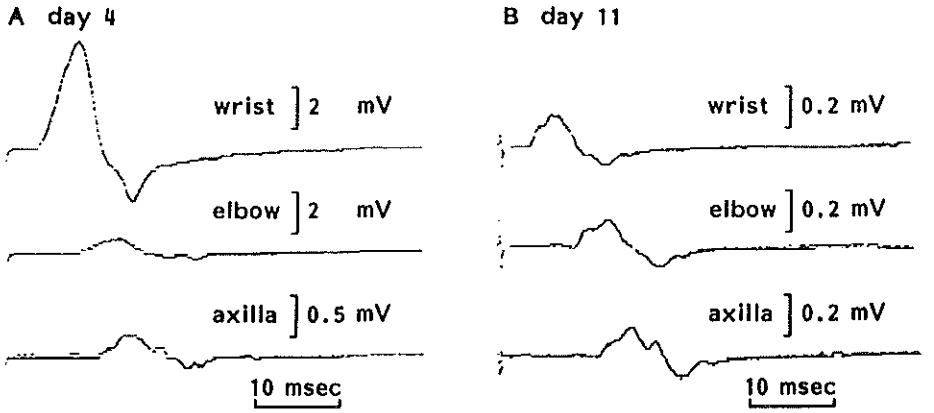


Fig. 8. CMAPs obtained in m. abductor pollicis brevis after stimulation of the median nerve at three levels, four (A) and eleven days (B) after onset of weakness. The patient was quadriplegic on both days. Note the different amplification scales.

Patient 6-8. The CMAPs were already low in the first study. Some length-dependent CMAP reduction could be demonstrated (table 21). This could not be explained in any case by dispersion of the amplitude comparing distal and proximal stimulation. These findings suggest, therefore, that some conduction block was present (Brown and Feasby, 1984). At the nadir these patients did not differ clinically from patients 1-5.

The sensory system (all patients)
The sensory system was unaffected clinically and not or minimally physiologically in 3 patients (nos.1, 7, 8,). In two more patiënts (nos.2 and 6) the sensory system became involved at a later stage, but was relatively spared as shown by the presence of small CSNAPs in nerves from which a motor response could no longer be obtained. In 3 patients (nos.3-5), all with conduction block in the motor nerves, the sensory system was involved both clinically and physiologically.

7.4 Discussion

Eight Guillain-Barré patients have been described, who developed severe axonal degeneration of the motor fibers. Although axonal degeneration is best determined by morphological criteria, this is in general not feasible in GBS-patients. Electrophysiological evidence of axonal degeneration, denervation potentials and CMAP decrease, is the second best parameter for axonal degeneration, but does not discriminate between degeneration of terminal nerve twigs and loss of complete axons. Moreover, distal demyelination can result in CMAP decrease just like axonal degeneration. This might occur in a subgroup of GBS patients (van der Meché et al., 1988). In the present study it was aimed to include only patients with severe loss of the motor axons and therefore the prerequisites were: 1. presence of dener-

vation potentials, 2. absent CMAP in at least some nerves and 3. slow clinical recovery suggestive of axonal regeneration.

The progress from early lesions to severe axonal degeneration was followed by means of longitudinal EMG studies. In the majority of patients (nos.1-5) the first study was characterised by significant conduction block. This was concluded from a "length-dependent CMAP amplitude reduction" of more than 25% without evidence for differential dispersion of the duration of the CMAPs. These findings are explained by lesions scattered along the nerve. From combined physiological and anatomical studies it was concluded that the causative lesion is demyelination (Feasby et al., 1986). Our observations suggest therefore, that in these patients demyelination occurred first and that this was followed by axonal degeneration. A further supportive argument for primary demyelination is that in other GBS-patients a similar conduction block has been observed, followed by rapid and complete recovery without the development of axonal degeneration (Brown and Feasby, 1984; van der Meché et al., 1988). Finally, observations in patient 5 demonstrated that conduction block can be followed by fast recovery in a part of the body (arms and left leg) suggestive of de- and remyelination while in another part (right leg) of the body of the same subject it can be followed by severe axonal degeneration. This observation makes it very likely that the initial lesion was also demyelinative in the extremity with axonal degeneration.

In a minority of patients (nos.6-8) only minimal conduction block could be detected and the CMAPs were already low in the first study. In these cases several mechanisms can be proposed: 1. the process is similar to the process in patiënts 1 - 5, but is more advanced at the time of the first EMG study; 2. distal demyelination, which has been suggested to occur in a group of GBS patients (van der Meché et al., 1988), is followed by axonal degeneration; 3. primary distal axonal degeneration occurred.

In general, it can be said that the processes determined in all patients can be explained by the same pathophysiological patterns as described before (van der Meché et al., 1988). Axonal degeneration might just reflect a more severe course of the disease. Also in experimental models of inflammatory polyneuropathy, it has been shown that a demyelinating mechanism may result in axonal degeneration in a dose dependent manner (Hartung et al., 1988). Alternatively, in these severely afflicted patients an additional "axonal" factor may be present, resulting in widespread axonal degeneration and contributing to conduction block. The possibility of a pure axonal mechanism has been suggested (Feasby et al., 1986), after studying 5 exceptionally severe GBS-patients. At the time of their first EMG's, however, the nerves were already inexcitable. Therefore, it is feasable that they may have missed an earlier demyelinating stage of the disease. Their one autopsy case, however, is very suggestive of primary axonal degeneration, although axonal degeneration following fulminant demyelination is difficult to exclude. This latter

Table 21. EMG studies of median, ulnar and peroneal nerve. W-res: worst result measured at either of the 3 studies.¶ MRC: force measured according to the Medical Research Council Scale.

Patient	1		2		3		4		5		6		7	8	
	1st study	W-res*	1st study	W-res*	1st study	W-res*	1st study	W-res*	1st study	W-res*	1st study	W-res*	1st study=W res*	1st study	W-res*
Day after onset	4	11	4	12	4	13	5	33	7	40	5	12	7	5	34
Median nerve															
APB (MRC)¶	0	0	0	0	4	0	3	0	2	0	3	0	0	0	0
CMAP-wrist (mV)	7.6	0.20	9.4	0	6.0	0.35	4.2	0	8.0	2.3	2.25	0	0.7	0	0
CMAP-elbow (mV)	0.75	0.18	1.3	0	5.2	0.20	3.0	0	4.0	0.25	1.75	0	0.3	0	0
DML (msec)	3.0	2.7	3.6	0	3.9	6.7	5.7	0	3.1	8.9	3.9	0	3.4	0	0
NCV (m/sec)	62	54	44	0	57	28.4	54	0	47	34	63	0	68	0	0
CSNAP-wrist (uV)	18	15	17	4	0	0	5	0	15	0	20	10	34	20	15
CSNAP-elbow (uV)	11	8	7	2	0	0	0	0	0	0	10	5	16	7	5
Ulnar nerve															
ADV (MRC)¶	0	0	0	0	4	0	3	0	1	0	2	0	0	0	0
CMAP-wrist (mV)	3	0	7.1	0	9.6	0.75	5.4	0	10.8	0.75	4.0	0	0	1.0	0
CMAP-elbow (mV)	0.4	0	3.6	0	8.1	0.75	2.3	0	5.1	0.65	4.0	0	0	0.8	0
CMAP-axilla (mV)	0.04	0	0.9	0	6.0	-	1.8	0	4.2	-	-	0	0	0.5	0
DML (msec)	3.3	0	2.9	0	3.2	7.2	4.0	0	2.2	7.4	3.6	0	0	2.4	0
NCV (m/sec)	54	0	60	0	68	28.3	43	0	45	15	50	0	0	62	0

CSNAP-wrist (uV)	17	18	11	2	5	0	0	0	5	0	20	10	22	20	15
CSNAP-elbow (uV)	10	7	6	-	0	0	0	0	0	0	15	5	9	10	5
CSNAP-axilla (uV)	7	5	-	-	0	0	0	0	0	0	7	-	6	5	-
Peroneal nerve															
CMAP-EDB-ankle (mV)	2.5	0.4	-	0	0.8	0	1.0	0	1.8	0	3.8	0	0.13	4.5	0.5
CMAP-TA-knee (mV)	0.5	-	-	0	-	-	-	-	-	0.3	-	-	0	-	-
Denervation	APB ++		APB ++		APB ++		APB +++		APB+		APB+++		APB++		APB+++
	Biceps ++		ADV ++		TA +		ADV +		T2+++		TA+++		TA++		TA+++
	TA ++		TA ++				TA +		Q+++						
	Q ++														

order of events has also been described recently in another autopsy case (Kanda et al., 1989). In our cases 6-8 we included a pure axonal form as the third option.

No sensory impairment, either clinically or physiologically was observed in patients 1, 7 or 8; a marked discrepancy was present in patients 2 and 6. Sparing of the sensory fibers has been described as occurring predominantly in patients with demyelinating lesions distributed along the length of the motor axons (van der Meché et al., 1988a, 1988b, 1989). If within nerve fascicles motor fibers are so severely affected that even the axons are damaged without affecting the adjacent sensory fibers, this suggests that axonal degeneration is not merely a bystander process, but restricted to already affected motor fibers. The paranodal area has been shown to be an important area for axon to myelin transport of molecules necessary for the assembly of myelin (Droz, 1979). Likewise it might be assumed that the axon is dependent on myelin-axon contact for its normal function. Indeed, in experimental models of demyelinating neuropathy it has been demonstrated that axonal function is altered after demyelination (Rao et al., 1981; Oikarinen and Kalimo, 1984).

Severe axonal degeneration is known to carry a bad prognosis (McLeod, 1981; Brown and Feasby, 1984; Albers et al., 1985; Feasby et al., 1986; Miller et al., 1987). Recently, however, attention has been drawn to low CMAPs as a general prognostic factor (Cornblath et al., 1988; Winer et al., 1988). A low CMAP, however, can be caused by distal demyelination without a concomitant severe clinical course (van der Meché et al., 1988a, 1988b). In contrast, a relatively high CMAP in the initial EMG may later be followed by severe axonal degeneration as shown in this study.
The timing of the EMG is, therefore, of importance. Miller et al (1988) (Miller et al., 1988) have suggested, that the ideal time may be 7 days after the nadir is reached. This, however, restricts the prognostic value of the CMAP early in the disease.

Chapter eight

General discussion

8.1 Introduction

The Dutch Guillain-Barré study has been a unique opportunity to study the results of electrodiagnostic testing in an early stage of the disease. A clinical follow-up of 6 months could further substantiate the initial diagnosis and, therefore, the electrodiagnostic studies may be regarded as having been performed in a group of GBS patients diagnosed on the basis of a clinical golden standard, independent of the electrodiagnostic study itself. For electrodiagnostic testing a rigid and relatively extensive protocol was designed. 90% Of the patients had weakness for 14 days or less at the first EMG and hence this first EMG can be regarded as a test early in the disease. The present study is the first one in which a rigid EMG protocol has been applied in an early stage of exclusively clinically defined GBS.

8.2 Findings and technical considerations

Electrodiagnostic abnormalities can be found in an early stage of GBS. At the first EMG the DMLs, CMAP amplitudes after distal stimulation and recruitment patterns on maximal voluntary effort showed the highest rate of abnormality. This is of great importance in the differential diagnosis of acute flaccid paresis, particularly if myotatic reflexes still persist as occurs occasionally in GBS. In general, the findings are in agreement with those found in other studies.
Parameters thusfar not studied systematically have been drawn from detailed analysis of CMAP measurement. Prolongued duration of the CMAP indicates dispersion in conduction velocities of individual fibers. This phenomenon is an important indicator of abnormality, if m-NCV or the DML are within normal ranges. As pointed out above, m-NCV and DML critically depend on the fastest fibers, and hence do not reflect conduction abnormalities in slower conducting fibers. CMAP dispersion in the presence of normal m-NCV and DML is a frequent finding in GBS.
CMAP reduction in a nerve traject is an almost exclusive electrodiagnostic sign of conduction block. However, there is much debate about the normal limits of CMAP reduction in healthy volunteers. A reduction of 50% has been mentioned as an upper limit of normal by some authors. This is in contrast to our experience, as is obvious from our reference values, which were collected from healthy volunteers. Therefore, we used limits specific for each of the motor nerves. If, however, the CMAP amplitude obtained after distal stimulation is already low, it becomes meaningless to express CMAP reduction as a percentage as measuring errors may vary up to 1 mV. To overcome false signs of conduction block due to the usual

measurement inaccuracies, we proposed to use the upper limit of normal or a difference of at least 1 mV as a limit for abnormal CMAP reduction. CMAP reduction may also be the result of phase cancellation due to abnormal temporal dispersion. This can be separated from pure conduction block if the duration of the CMAP is taken into account. Both phenomena, however, are a result of demyelination. Therefore, for diagnostic purposes, we applied CMAP reduction regardless of CMAP duration. Obviously, at least two stimulation points are nessecary to show the presence of CMAP reduction. However, usually the most proximal parts of the nerve trajectory are not accessible for supramaximal surface stimulation, whereas extreme distal stimulation CMAP recording is obscured by stimulus artifact. As a consequence CMAP changes over these most distal and proximal stretches can not be detected. This is a major drawback, because notably these sites have been suggested to harbour conduction deficits, at least in part of the patients. Particularly the low CMAP amplitudes, which occur frequently in an early stage of the disease, defy further analysis by standard electrodiagnostic techniques. As a consequence it is, as yet, impossible to discriminate electrophysiologically distal demyelination from axonal degeneration as a cause of low CMAP amplitudes. However, biophysical and immunological arguments exist, which suggest the presence of distal conduction block in GBS.
The present study stresses the importance of sound technical methodology. Particularly CMAP measurement is prone to pitfalls as discussed in chapter 2. In general a substantial variability is found among normal individuals, and this may well be the reason why CMAP measurement has been neglected so long. Therefore, it is important to collect reference values for each laboratory as different electrodes and electrode placement lead to different limits of normal. We have shown that, when proper reference values are obtained, and attention is being paid to possible pitfalls, reliable and diagnostically inportant conclusions can be derived from CMAP analysis. Hence, we suggest, that CMAP measurement (with surface electrodes) is routinely performed in every EMG laboratory.

8.3 Criteria and prognostic value

We developed *criteria for polyneuropathy and for demyelination.* The effectiveness of these criteria was tested in 135 patients with clinically proven GBS. An extremely high sensitivity and specificity for GBS patients in an early stage of the disease was obtained by requiring a minimal number of abnormal variables in more than one nerve. The criteria for demyelination, however, scored less well. This may be explained by the patchy localisation of abnormalities throughout the nerve and by the fact that testing of CMAP reduction cannot be applied to every segment, particularly not the most distal and proximal segments of the peripheral nerve. This will probably have caused a serious underestimation of the incidence of CMAP reduction. Therefore, lack of fullfilling the criteria does not exclude demyelination. Validation of the criteria for polyneuropathy has to be performed in

other kinds of polyneuropathy; the sensitivity of criteria for demyelination has to be analysed further in patients with motor neuronopathies in the future.
Among the electrodiagnostic variables analysed, CMAP amplitude and recruitment pattern on maximal voluntary effort, turned out to be significant *prognostic factors* in GBS. However, in individual patients, one has to be careful because many patients, in whom low CMAP amplitudes are found, may recover satisfactorily. As described, low CMAP amplitudes may reflect conduction block due to demyelination as well as axonal degeneration. They cannot be separated electrodiagnostically, but they have very different outcomes. Furthermore, one has to bear in mind, that for a function like walking proximal muscles are more important than distal muscles which are generally used for CMAP measurement. The important finding, that the recruitment pattern in distal muscles has considerable prognostic value, would thus suggest an ever more important role for recruitment testing in proximal muscles. This has to be evaluated in future studies.

8.4 Electrophysiological subtypes

Clinically, GBS is defined as a more or less symmetrical polyneuropathy. Pathological observations show a variability between patients in the localisation of lesions; widespread lesions as well as lesions typically confined to nerve roots and predominant injury of intramuscular nerve twigs, may be discerned. A similar subdivision has been proposed by electrophysiological studies. Some pathophysiological findings have made it likely that parts of peripheral nerves may be differentially injured. Furthermore, the usual compression sites may be more vulnerable. At the level of the roots, the intramuscular nerve twigs and at the usual compression sites it is generally assumed that the blood nerve barrier is either absent or deficient. Therefore, these sites are particularly prone to demyelination due to humoral factors. Proximal and distal lesions may result in specific electrophysiological changes as is summarised in table 22. More diffuse or random lesions result in random conduction block. Such diffuse lesions imply breakdown of the bloodnerve barrier or threspassing of previously activated T-cells through intact blood nerve barrier.
It would seem attractive to subdivide GBS patients into three groups (proximal, diffuse and distal) according to the predominant site of injury (table 22). However, both an attempt to categorise patients according to this scheme and a formal cluster analysis failed to discern the existence of these simple categories. Therefore, we have to conclude to the existence of an electrophysiological continuum. However, we do not know whether this continuum results from the limitations of our electrodiagnostic parameters or that this continuum is a true reflection of the sum effect of underlying pathophysiological factors. It is conceivable that the inherent limitations of our electrophysiological parameters obscure the possible existence of true pathophysiological subgroups in terms of a predominant site of injury. Some of these parameters preclude unequivocal interpretation in terms of localisation.

Recruitment pattern will always be abnormal irrespective where conduction block occurs along the nerve; it is the electrophysiological counterpart of clinical paresis.

Table 22.

predominant site	DML	m-NCV	F-lat	CMAP dist.	CMAP reduction	pattern
prox	=	=	↑	=	=	↓
intermediate/diffuse	=	=/↓	=	=	↓	↓
distal	↑	=	=	↓	=	↓

DML: distal motor latency; m-NCV: motor nerve conduction velocity; F-lat: F-latency if DML and m-NCV are normal; CMAP dist.: CMAP amplitude after distal stimula-tion; CMAP dacay: CMAP amplitude reduction after proximal stimulation compared to distal stimulation; pattern: recruitment pattern after maximal voluntary effort.

As pointed out before, DML and NCVs may be quite normal or near normal as long as the fastest fibers are spared and are therefore not a very sensitive indicator of abnormalities. Moreover predominant distal location of conduction abnormalities will obscure abnormalities occuring at more proximal sites. For instance, if conduction block is present distally with very low CMAPs, then detection of intermediate conduction block will be very difficult, because below a certain level of distal CMAP amplitude further reduction cannot be detected anymore. How distal conduction block may defy more proximal demyelination, is nicely illustrated by patients that on the first examination show length dependent CMAP reduction, but subsequently develop equally low CMAPs for distal as for proximal stimulation. An excessive increase of distal conduction block compared to conduction block more proximally may be due to a higer vulnerability at the level where the axon branches into the terminal twigs and at the transition of myelinated to unmyelinated endings. As a result, in patients with low distal CMAPs from onset onward one can not differentiate between axonal degeneration and distal conduction block. Nor is it possible to differentiate between axonal degeneration limited to the distal motor twigs alone or degeneration throughout the whole nerve. Because of these limitations it is not surprising that these electrodiagnostic parameters fail to discriminate subgroups on a basis of predominant site of nerve injury.
Therefore in the search for subtypes it would be more appropriate to reverse the problem and look whether electrodiagnostic characteristics correlate with any clinical, pathological or immunological subtypes of GBS. Such studies are now in progress.

8.5 Future research

One of the most important projects in the near future will be the further evaluation of the electrodiagnostic criteria. First of all the sensitivity of the criteria for polyneuropathy have to be tested in other polyneuropathies like diabetic neuropathy. Additionally the specificity of the criteria for primary demyelination have to be tested in patients with purely axonal motor neuron disorders. Furthermore, it is desirable to test the effectiveness of the electrodiagnostic criteria presented here, in GBS patients less afflicted than the in this study, none of whom were able to walk independently at entry.

Distal demyelination versus axonal degeneration as two causes for a low distal CMAP can not be separated with conventional conduction studies. Measurement of twitch tensions may possibly differentiate between the two by comparing twitch tension after distal nerve stimulation and motor point stimulation.

Given the prognostic value of recruitment pattern measurements in distal muscles, this parameter should be evaluated for proximal muscles, as proximal muscle power is perhaps even more correlated with functional outcome. Recruitment pattern can easily be performed, whereas proximal muscles are not easily accessible for conduction studies.

Finally, the awaited further differentiation of immunological subtypes of GBS patients have to be correlated with electrodiagnostic parameters in order to elucidate the underlying pathophysiological mechanisms. This may further substantiate the as yet uncertain existence of electrodiagnostic subtypes.

General summary

The aim of this study was to describe several aspects of electrodiagnostic testing in the acute stage of the Guillain-Barré syndrome.

In *chapter one a general description of the Guillain-Barré syndrome* is given with respect to the clinical, pathological and immunological features; additionally the therapeutical options are discussed. The design of the Dutch Guillain-Barré trial is introduced and the main questions of this electrodiagnostic study are put forward.

Chapter two describes the *electrophysiology of nerve conduction in normal and abnormal fibers*, and continues with *principles and interpretation of motor conduction studies in patients with polyneuropathy*. The importance of CMAP analysis in demyelinating polyneuropathy is explained and the technical aspects of CMAP maesurements, including the avoidence of pitfalls, is discussed.

In *chapter three* the *literature* concerning electrodiagnostic testing in Guillain-Barré syndrome is reviewed. Since Lambert's original report in 1960, several important electrodiagnostic findings have been reported repeatedly. These include the presence of low CMAP amplitudes early in the disease, which reflect conduction block, as well as conduction slowing somewhat later in the disease. Other important esthablished features if GBS consist of the appearence of axonal degeneration and in severe cases "inexcitable motor nerves". However, electrodiagnostic studies of GBS often show conflicting results. This may be due to the variability in clinical severity, the patchy distribution of lesions, different timing of the studies and technical aspects of the electrodiagnostic studies.

In *chapter four* the *electrodiagnostic findings and patterns of this study* are described. 135 Patients were prospectively followed with 3 EMG's. The first EMG was performed with a median delay of 6 days after onset of the disease followed by an examination one and four weeks later. The distal motor latencies and the CMAPs, after distal stimulation of upper limb nerves, were most often abnormal (> 80%). Decrease of nerve conduction velocity, abnormal dispersion of the CMAP, abnormal reduction of the CMAP with more proximal stimulation and recruitment pattern were abnormal in about half of the patients. For the whole group, the abnormal parameters found at the first examination changed little over the second and third EMG, the only exeption being the presence of denervation potentials, that increased over time. However, in individual patients changes do occur and therefore the EMG at the nadir was found to be most relevant clinically. Subgroup analysis either using a paradigm described before or using a formal cluster analysis did not reveal subgroups as an explanation of the observed pathophysiological variability. It is concluded that a continuum of pathophysiological abnormalities exists and that this may reflect also a spectrum of immune mechanisms variably playing a role in the individual patient.

Chapter five describes the development of *electrodiagnostic criteria* for the detection of polyneuropathy and demyelination. 85% of Guillain-Barré patients fulfilled criteria for polyneuropathy in the first EMG (mean time inteval 6 days after onset of the disease), whereas none of 45 healthy volunteers did. The sensitivity and specificity of these criteria and also the criteria published by others were tested in 135 Guillain-Barré patients all in an early stage of the disease. They were all included in the Dutch Guillain-Barré trial. Different sets of electrodiagnostic criteria for polyneuropathy and demyelination have been suggested, but such criteria have never been formally tested. We formulated in this study algorithms consisting of sets of selected electrodiagnostic parameters, which, individually, are generally accepted indicators of abnormality. The proposed criteria for demyelination were fulfilled in 60%, 66% and 72%, respectively, in three consecutive EMGs, performed within one month of onset; again, this was not the case in any of the healthy volunteers. By using criteria published before by others, the sensitivity of electrodiagnostic testing was generally considerably lower. Further studies are necessary, to test sensitivity and specificity of these criteria in GBS versus other polyneuropathies and motor neuropathies.

In *chapter six* the *prognostic value* of electrodiagnostic tests is described. Independent locomotion 8 weeks and 6 months after entry were considered to be the outcome measures of most clinical value. Electrodiagnostic data obtained one week after entry were concluded to be most important for studying prognostic value. This has been attributed to the fact that 87% of the patients were at the nadir of their disease at that moment. In univariate analysis, CMAP amplitudes of thenar and hypothenar muscles obtained after distal and proximal stimulation, as well as the recruitment pattern on maximal voluntary effort in all three tested muscles, were significant predictors for outcome 8 weeks and 6 months after entry in the study. Motor nerve conduction velocity and distal motor latencies of ulnar and median nerves were weak predictors of outcome at 8 weeks after entry. In multivariate analysis the hypothenar CMAP amplitude on distal stimulation and recruitment pattern of abductor digiti minimi muscle both had an independent predictive value for independent locomotion 8 weeks after entry.

Chapter seven describes aspects of *severe axonal degeneration* which occasionally occurs in Guillain-Barré patients, and often results in permanent functional deficit. In order to assess the development of axonal degeneration, a consecutive series of 42 patients was followed longitudinally using clinical and neurophysiological methods. Eight patients were considered to suffer from severe axonal degeneration: in these 8 patients denervation potentials were eventually found and at least one nerve proved inexcitable. Clinical recovery was slow and incomplete. Five of these eight patients initially showed a pronounced conduction block, the physiological hallmark of demyelination, before signs of axonal degeneration developed. In the remaining three patients, the first evaluation revealed low amplitudes with only modest conduction block; this is consistent with predominantly distal demyelination, but might, alternatively, be explained by primary axonal degeneration. In

general we conclude that severe axonal degeneration is likely to be preceeded by demyelination. Therefore, at present is not necessary to propose a seperate subgroup of axonal GBS. Axonal involvement may partly reflect more severe clinical course with fulminant demyelination with an excess of bystander axonal degeneration.

Chapter eight is the general discussion in which also suggestions are made for future research.

Samenvatting

Het doel van de dit proefschrift is het beschrijven van de electrodiagnostische aspecten van het Guillain Barré syndroom in de acute fase.

In het *eerste hoofdstuk* wordt een algemene beschrijving gegeven van het Guillain-Barré syndroom, inclusief de klinische, pathologische, immunologische en therapeutische aspecten. Tevens wordt het ontwerp van de Nederlandse Guillain-Barré trial kort besproken. De belangrijkste electrodiagnostische vraagstellingen van deze studie worden gepresenteerd.

Hoofdstuk twee beschrijft de electrofysiologie van de zenuwgeleiding in normale en abnormale zenuwvezels, ter introductie tot de principes en interpretatie van motorisch zenuwgeleidingsonderzoek bij patiënten met polyneuropathie. De meest belangrijke parameter bij onderzoek van polyneuropathieën is de CMAP; de meeste pitfalls kunnen worden voorkomen door het onderzoek nauwgezet uit te voeren.

In *hoofdstuk drie* wordt de literatuur betreffende electrodiagnostisch onderzoek van het Guillain-Barré syndroom besproken. Sedert de publicatie van Lambert, daterend uit 1960, zijn veranderingen in verschillende belangrijke electrodiagnostische variabelen gerapporteerd: vroeg in de ziekte komt geleidingsblokkade voor, welke zich uit in afname van CMAP-amplitudes en, in het algemeen wat later tijdens ziekte, geleidingsvertraging. De electrodiagnostische bevindingen zijn in de literatuur echter vaak met elkaar in tegenspraak. Mogelijk wordt dit veroorzaakt door de variabiliteit van de klinische ernst, de vlekkige verdeling van de afwijkingen in het perifere zenuwstelsel, verschillende tijdstippen van onderzoek ten opzichte van het ontstaan van de ziekte en door de technische aspecten van het electrodiagnostische onderzoek. In de meeste publicaties echter worden geleidingsvertraging, geleidingsblokkade, axonale degeneratie en, in ernstige gevallen, onprikkelbare motorische zenuwen beschouwd als de meest belangrijke electrodiagnostische bevindingen van het Guillain-Barré syndroom.

In *hoofdstuk vier* worden de electrodiagnostische bevindingen beschreven. 135 Guilain-Barré patiënten werden longitudinaal met drie EMG's onderzocht. Het eerste EMG werd gemiddeld zes dagen na ontstaan van de ziekte verricht, de volgende EMG's een week en vier weken na het eerste. De distale motorische latentietijden en de CMAP amplituden verkregen na distale stimulatie van armzenuwen waren de meest frequente abnormale variabelen (> 80%). Geleidingsvertraging, abnormale dispersie van de CMAP, abnormale reductie van de CMAP amplitude bij meer proximale stimulatie en het aanspanningspatroon waren in 50% van de gevallen afwijkend. Voor de gehele groep patiënten werden opmerkelijk weinig veranderingen vastgesteld in de variabelen gedurende de follow-up van drie EMG's; een uitzondering vormde de denervatie activiteit die toenam in de tijd. In individuele patiënten deden zich wel veranderingen voor; electrodiagnostisch

onderzoek vroeg in het nadir verricht is het meest informatief. Onderzoek naar het voorkomen van subgroepen ofwel gebruik makend van de eerder beschreven paradigma, ofwel volgens formele cluster-analyse, heeft tot de conclusie geleid, dat er een continuüm van pathofysiologische afwijkingen is als uiting van een spectrum van immunologische mechanismen, welke in individuele patiënten aanwezig kunnen zijn.

In *hoofdstuk vijf* wordt de constructie van electrodiagnostische criteria voor de detectie van polyneuropathie en demyelinisatie beschreven. Vijfentachtig procent van de Guillain-Barré patiënten voldeden aan de criteria voor polyneuropathie in het eerste EMG (gemiddeld zes dagen na ontstaan van de ziekte); dit in tegenstelling tot 45 gezonde vrijwilligers. De sensitiviteit en specificiteit van deze criteria en ook van de criteria door anderen gepubliceerd, werden in 135 Guillain-Barré patienten getest, die in een vroeg stadium van de ziekte verkeerden. Ze maakten allen deel uit van de Nederlandse Guillain-Barré trial. Verschillende sets van electrodiagnostische criteria voor polyneuropathie en demyelinisatie zijn voorgesteld, maar werden niet formeel getest. Wij formuleerden in dit onderzoek algoritmen, bestaande uit sets van geselecteerde electrodiagnostische parameters, die individueel algemeen geaccepteerde maatstaven zijn voor afwijkingen in de zenuwgeleiding. Aan voorgestelde criteria voor demyelinisatie werd voldaan in 60%, 66% en 72%, respectievelijk in de drie opeenvolgende EMG's, verricht in de eerste maand van de ziekte; dit wederom in tegenstelling tot de gezonde vrijwilligers die niet voldeden aan de criteria. Toepassing van eerder door anderen gepubliceerde criteria resulteerde in lagere sensitiviteit van de electrodiagnostische tests. Verder onderzoek is noodzakelijk om de sensitiviteit en specificiteit van deze criteria te testen ten opzichte van andere polyneuropathieën en ten opzichte van motorische neuropathieën.

In *hoofdstuk zes* wordt de prognostische waarde beschreven van electrodiagnostisch onderzoek in het Guillain-Barré syndroom. Lopend zonder steun acht weken en zes maanden na entry in de trial werden beschouwd als de meest waardevolle eindpunten in klinische zin. Electrodiagnostische data verkregen één week na entry, werden beschouwd als de meest relevante voor onderzoek naar prognostische waarde. Dit werd ondersteund door het feit dat 87% van de patiënten op dat moment in hun klinisch nadir verkeerden. Na univariate analyse bleken CMAP amplitudes van thenar en hypothenar verkregen na distale en proximale stimulatie zowel als het aanspanningspatroon in alle onderzochte spieren significante predictieve waarde te hebben voor beide eindpunten. Motorische zenuwgeleidingssnelheden en distale motorische latentietijden van armzenuwen, bleken zwakke predictieve waarde te hebben voor het eind op acht weken. Na multivariate analyse bleek de hypothenar CMAP amplitude verkregen na distale stimulatie in het aanspanningspatroon van de musculus abductor digiti minimi beiden onafhankelijke predicitieve waarde te hebben voor lopen zonder steun acht weken na entry.

In *hoofdstuk zeven* worden aspecten beschreven van ernstige axonale degeneratie die zich soms voordoet in Guillain-Barré patiënten, wat vaak blijvende invaliditeit tot gevolg heeft. Teneinde de ontwikkeling van axonale degeneratie te kunnen vaststellen, werden 42 Guillain-Barré patiënten longitudinaal klinisch en electrodiagnostisch onderzocht. Acht patiënten hadden verschijnselen van ernstige axonale degeneratie: denervatie potentialen, tenminste één onprikkelbare zenuw, klinisch langzaam en incompleet herstel. Vijf van deze acht patiënten hadden aanvankelijk uitgesproken geleidingsblokkade, een typisch verschijnsel van demyelinisatie, voordat zich tekenen van axonale degeneratie openbaarden. In de overige drie patiënten werd aanvankelijk lage CMAP amplituden met slechts bescheiden geleidingsblokkaden aangetroffen. Dit is in overeenstemming met predominante distale demyelinisatie, maar kan in tegenstelling hiermee ook berusten op primaire axonale degeneratie. Over het algemeen kan geconcludeerd worden, dat ernstige axonale degeneratie voorafgegaan kan worden door demyelinisatie. Daarom is op dit moment de veronderstelling van een axonale vorm van het Guillain-Barré syndroom als een aparte groep niet houdbaar. Axonale schade kan beschouwd worden als bystander-effect van zeer ernstige demyelinisatie.

Hoofdstuk acht bevat de algemene discussie, waarin ook suggesties worden gedaan voor verder onderzoek.

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Appendix I: Clinical criteria (Asbury, 1990)

I. Features Required for Diagnosis
   A. Progressive motor weakness of more than one limb. The degree ranges from minimal weakness of the legs, with or without mild ataxia, to total paralysis of the muscles of all four extremities and the trunk, bulbar and facial paralysis, and external opthamoplegia.
   B. Areflexia (loss of tendon jerks). Universal areflexia is the rule, though distal areflexia with definite hyporeflexia of the biceps and knee jerks will suffice if other features are consistent.

II. Features Strongly Supportive of the Diagnosis
   A. Clinical features (ranked in order of importance)
      1. Progression. Symptoms and signs of motor weakness develop rapidly but cease to progress by four weeks into the illness. Approximately 50% will reach the nadir by two weeks, 80% by three weeks and more than 90% by four weeks.
      2. Relative symmetry. Symmetry is seldom absolute, but usually, if one limb is affected, the opposite is as well.
      3. Mild sensory symptoms or signs.
      4. Cranial nerve involvement. Facial weakness occurs in approximately 50% and is frequently bilateral. Other cranial nerves may be involved, particular innervating the tongue and muscles of deglutition, and sometimes the extra ocular motor nerves. On occasion (less than 5%), the neuropathy may begin in the nerves of the extraocular muscles or other cranial nerves.
      5. Recovery. It usually begins two to four weeks after progression stops. Recovery may be delayed for months. Most patients recover functionally.
      6. Autonomic dysfunction. Tachycardia and other arrythmias, postural hypotension, hypertension, and vasomotor symptoms, when present, support the diagnosis. These findings may fluctuate. Care must be exercised to exclude other bases for these symptoms, such as pulmonary embolism.
      7. Absence or fever at the onset of neuritic symptoms. Variants (not ranked)
         1. Fever at ontset of neuritic symptoms.
         2. Severe sensory loss with pain.
         3. Progression beyond four weeks. Ocassionally, a patient's disease will continue to progress for many weeks longer than four or the patient will have a minor relapse.
         4. Cessation of progression without recovery or with major permanent residual deficit remaining.

5. Sphincter function. Usually the sphincters are not affected, but transient bladder paralysis may occur during evolution of symptoms.
6. Central nervous system involvement. Ordinarily, Guillain-Barré syndrome is thought of a disease of the peripheral nervous system. Evidence of central nervous system involvement is controversial. In occasional patients, such findings as severe ataxia interpretable as cerebellar in origin, dysarthria, extensor plantar responses, and ill-defined sensory levels are demonstrable, and these need not exclude the diagnosis if other features are typical.

B. Cerebrospinal fluid features strongly supportive of the diagnosis.
   1. CSF protein. After the first week of symptoms, CSF protein is elevated or has been shown to rise on serial lumbar punctures.
   2. CSF cells. Counts of 10 or fewer mononuclear leukocytes/mm^3 in CSF.

Variants
1. No CSF protein rise in the period of one to ten weeks after the onset of symptoms (rare).
2. Counts of 11 to 50 mononuclear leukocytes/mm^3 in CSF.

C. Electrodiagnostic features strongly supportive of the diagnosis.
   Approximately 80% will have evidence of nerve conduction slowing or block at some point during the illness. Conduction velocity is usually less than 60% of normal, but the process is patchy and not all nerves are affected. Distal latencies may be increased to as much as three times normal. Use of F-wave responses often gives godd indication of slowing over proximal portions of nerve trunks and roots. Up to 20% of patients will have normal conduction studies. Conduction studies may not become abnormal until several weeks into illness.

III. Features Casting Doubt on the Diagnosis
   1. Marked, persistent asymmetry of weakness.
   2. Persistent bladder or bowel dysfunction.
   3. Bladder or bowel dysfunction at onset.
   4. More than 50 mononuclear leukocytes/mm^3 in CSF.
   5. Presence of polymorphonuclear leukocytes in CSF.
   6. Sharp sensory level.

IV. Features That Rule Out the Diagnosis
   1. A current history of hexacarbon abuse (volatile solvents; n-haxane and methyl n-butyl ketone). This includes paint lacquer vapors or addictive glue sniffing.

2. Abnormal porphyrin metabolism indicating a diagnosis of acute intermittent porphyria. This would manifest as increased excretion of porphobilinogen and delta-aminolevulinic acid in the urine.
3. A history or finding of recent diphtheritic infection, either wound, with or without myocarditis.
4. Features clinically consistent with lead neuropathy (upper limb weaknesws with prominent wrist drop; may be asymetrical) and evidence of lead intoxication.
5. The occurence of a purely sensory syndrome.
6. A definite diagnosis of a condition such as poliomyelitis, botulism, hysterical paralysis, or toxic neuropathy (e.g., from nitrofurantoin, dapsone, organophosphorus compounds), which occasionally may be confused with Guillain-Barré syndrome.

Appendix II: The electrodiagnostic protocol applied in the Dutch Guillain-Barré trial

NERVE CONDUCTION STUDIES

STIMULATION

Surface electrodes are to be used for stimulation. Prefered stimulation duration: 0.3 msec.

Supramaximal stimulation is obtainted by searching for the optimal site at low stimulus strength. Then the stimulus strength is increased to supramaximal level. Sometimes a high stimulus strength is needed.

Minimal distance of stimulation sites proximal and distal over knee and elbow > 7 cm.; preferably 10 cm.

RECORDING

Motor responses:

Ag - AgCl electrodes (diam. 9 mm) are used in a tendon-belly montage.

Position of the indifferent electrodes:

M.APB and M.ADV: the carpophalangeal joint (I)

M.EDB: the tarsophalangeal joint (V)

After positioning the indifferent electrode, the "active" electrode is used to search for the optimal position of the searching electrode. This is esthablished as soon as:

the CMAP-amplitude is maximal;

has the steepest negative deflection;

has the shortest duration.

The electrodes have to be fixed properly with adhaesive tape and electrode paste.

Sensory responses: (antidromically evoked)

Dig. II and Dig. V ring surface electrodes; placed 2,5 cm. apart with the proximal electrode at the first intraphalangeal joint.

N.suralis: surface electrodes "Medelec, blue type" with inter-electrode distance of 3 cm; placed at the malleolus lateralis; stimulation site 12 cm. proximal from recording electrode at the calf.

F-responses:

Obtainted from a series of 20 stimuli (cathode in proximal direction). Check for the maximal evoked CMAP before and after.

*Filter settings**

sensory amplitude : 10 Hz.- 2 kHz.

motor amplitude : 2 Hz.-10 kHz.

*Timebase**

Sensory potentials : 2 or 5 msec./div.
motor potentials : 5 msec./div.

Amplification:

Such, that the evoked CAP is projected over several screen divisions.

MEASUREMENT OF PARAMETERS

CMAP amplitude top-top in mV (± 0,1 mV)
latency in msec. (± 0,1 msec.)
duration neg.potential above baseline in msec. (± 0,1 msec.)
CNSAP amplitude top-top in mV (± 0,1 uV)
latency in msec. (± 0,1 msec.)
duration of negative part of the potential above baseline in msec. (± 0,1 msec.)
distances in cm. (± 0,5 cm.)

TEMPERATURE

Skin surface temperature of all stimulation and recording sites (± 0.5 °C).
All conduction velocities will be corrected for temperature by the coordinating centre.

MYOGRAPHY

With the concentric needle electrode the muscle has to be tested for:

recruitment pattern on maximal voluntary effort;
denervation activity;
fibrillation and positive sharp waves, rated as follows: 0 = not present; + = some; ++ = many; +++ = baseline completely occupied.
motor unit potential characteristics.

FOLLOW UP:

First EMG: within two days after randomisation;
Second EMG: one week after randomisation;
Third EMG: four weeks after randomisation.

Nerves to be tested:

Motor nerves (recording sites between parenthesis).
Ulnar nerve stimulation; at wrist, distal and proximal of elbow, sulcus bicipitalis (M.ADV).
Median nerve stimulation; at wrist and elbow (M.APB) facultatively:
Peroneal nerve stimulation; at ankle, distal and proximal of fibular head (M.EDB).

Sensory nerves (recording sites betwee parenthesis).
Ulnar nerve stimulation wrist, distal and proximal of elbow, sulcus bicipitalis (Dig. V)
Sural nerve stimulation at calf (ankle).

F-responses:
Ulnar and median nerve with stimualtion at the wrist (M. ADV respectively M. APB);
Peroneal nerve with stimulation at ankle (M.EDB).

Muscles to be tested electromyographically:
M. APB; M. ADV; M.TA.

* or the most nearby settings

Appendix III: An example of the datasheet

NAME: FOLLOW "P (1)/ 2 / 3 : date: 31-8-88 TRIAL NUMBER: 0 8 2

TMG REG.NR. INVESTIGATORS

STIMULATION nerve: local.:	REGISTRATION local.:	ampl.	lat. msec.	lat. Δ	dur. msec.	dist. cm.	temp. °C	DML ncv	DML ncv corr.	F-responses (20 trials) min. N. lat.	F-responses (20 trials) max. lat.	F-responses (20 trials) max. ampl.	myography	myography	clin.
	M.APB.	3 mV	3.3		10 msec	6	31.0	5.3	4.3				pattern: O-SP-MP-IP	reduct.: (+)	
M.MED. WRIST		3 mV	8.7	4.4	10	25	31.5	51	64	8	28	250 µV		polyfasia: (−)	MRC: 4
E/r ELBOW															
	DIG.II														
M.MED. WRIST		65 µV	3.5		3 msec	16	28.5	46	58						TPD:
E/r ELBOW		–													PS:
UP.ARM		–													
	M.ADV														
M.ULN. WRIST		3 mV	2.8		12	7	36.5	2.8	2.2	10	198	300 µV	pattern: O-SP-(M)-IP	reduct.: (+)	
E/r DIST.ELBOW		3 mV	6.9	4.1	12	19	32	46	52	–	–	–		polyfasia: (−)	MRC: 4
PROX.ELBOW		3 mV	8.7	5.9	12	28	34	47	44	–	–	–			
UP.ARM		3 mV	10.4	7.3	12	34	34.5	47	48	–	–	–			
	DIG.V							43							
M.ULN. WRIST		20 µV	2.5	4.1	5	11	29	~~7.8~~	55						TPD:
E/r DIST.ELBOW		10 µV	6.4		5	19	32	49	54						PS:
PROX.ELBOW		8 µV	8.8	5.3	5	28	34	53	55						
UP.ARM		8 µV	9.7	7.3	5	34	34.5	47	48						
	M.EDB	1.2 mV	6.0		15	7	29.5	6.0	4.1	0	0	0			
*M.PER. ANKLE		300 µV	12.3	6.3	20	31	30.0	46	54	–	–	–			
E/r DIST.KNEE		300 µV	14.2	1.5	20	10.5	61.5	10	15	–	–	–			
PROX.KNEE															
	N.TA												pattern: O-SP-MP-IP	reduct.: (+)	MRC: 3
*M.PER. DIST.KNEE														polyfasia: (−)	
I/r PROX.KNEE															
	MAL.LAT.														
*M.SUR. ANKLE															PS:
I/r M.V.															

Distance CP - M.ADV: cm. Comments:

*Only if the result of the arm study is normal

Appendix IV:

The following persons and institutions participated in the Dutch Guillain-Barré Study Group. An asterisk indicates those who performed electrodiagnostic testing. Co-ordinating center: University Hospital Dijkzigt, Erasmus University, Rotterdam. Clinical co-ordinator: R.P. Kleyweg, neurologist. E.M.G. co-ordinator: J. Meulstee*, neurologist. Organisation trial office: R.M. van den Hoven.
Monitoring Committee: F.G.A. van der Meché, neurologist, (chairman), H.F.M. Busch, neurologist, R.P. Kleyweg, neurologist, M.L. Lee, statistician, J. Meulstee, neurologist, P.I.M. Schmitz, statistician.
Other centers: ranked according to the number of patients randomised. Academisch Ziekenhuis Groningen, A.E.J. de Jager, T.W. van Weerden*. Academisch Ziekenhuis Utrecht, P.L.Oey*, J.P. Ter Bruggen. Academisch Medisch Centrum, Amsterdam, J. Stam, B.W. Ongerboer de Visser*. De Wever Ziekenhuis, Heerlen, C.L. Franke, J.W. Vredeveld*. Westeinde Ziekenhuis, Den Haag, W.F.M. Arts, E.J. Jonkman*, A.W. de Weerd*. St. Josephziekenhuis, Eindhoven, B.J. van Kasteren*. Academisch Ziekenhuis bij de Vrije Universiteit, Amsterdam, J.J. Heimans, C. Polman, R.P.M. Strijers*. Ver. Ziekenhuizen Ziekenzorg, Enschede, E.M. de Vries - Leenders*, E.N.H. Jansen. Canisius-Wilhelmina Ziekenhuis, Nijmegen, C.W.G.M. Frenken, W.I.M. Verhagen*. St. Clara Ziekenhuis, Rotterdam, H.J. v.d. Brand*, H.A.W. Sinnige. Medisch Centrum Alkmaar, J.A. van Leusden*. St. Elisabeth Ziekenhuis, Tilburg, A.A.W. Op de Coul, R.L.A.A. Schellens*. St. Ziekenhuis Westelijke Mijnstreek, Sittard, J.J.Korten. Ziekenhuis Leijenburg, Den Haag, L.G.F. Sinnige, D.L.J. Tavy*, A.K. Wattendorf. Academisch Ziekenhuis Maastricht, C.J. Höweler, F. Spaans*.

Appendix V:

Reference values.

Methods.

Nerve conduction studies were performed in a warm temperature controlled room (30° Celsius), surrounded by a cage of Faraday. All tests were performed using a Nicolet Viking type 1 Myograph. Single supramaximal stimuli were delivered using standard surface stimulator electrodes (diameter 5 mm; interelectrode distance of 25 mm) with cathode located distally. Stimuli were delivered supramaximally guided by configuration of evoked motor responses, and consisted mostly of rectangular pulses of 0.3 msec. and 20 mA through in constant current stimulator. For motor responses, recording electrodes consisted of surface disk electrodes (diameter 10 mm), attached to the skin with electrode jelly and adheasive tape. For ulnar, median and peroneal nerve abductor digiti quinti (M. ADV.), abductor pollicis brevis (M. APB.) and extensor digitorum brevis (M. EDB.) were used, respectively. Optimal recording sites of motor responses were searched for carefully, under guidance of the CMAP configuration, such, that a maximal amplitude, a steepest possible initial negative deflection and a shortest possible duration of the negative part of the CMAP emerged.
In each of the 45 volunteers ulnar, median and peroneal nerves were tested. The ulnar nerve was stimulated at the wrist and distal of the ulnar sulcus. The median nerve was stimulated at the wrist and at the elbow. The peroneal nerve was stimulated at the ankle, distal and proximal of the fibular head.
Of all motor responses top-top amplitude, the duration and area of the negative phase and the onset latency of the CMAP were measured. Ratios of amplitudes, duration and areas of motor responses after stimulation of all stimulus sites were computed. Distances between stimulation sites and recording sites were measured with an accuracy of 5 mm, after which motor nerve conduction velocity was measured. All nerve conduction velocities were transformed to a reference temperature of 35° Celsius after measuring the skin temperature using a thermocouple (Tempcontrol,type 2003) (Geerlings and Mechelse, 1985).
Minimal latency of f-responses were obtained after 20 trials, under guidance of the optimal CMAP after distal stimulation.
After collection data were fed into a database and the results were analysed using "STATA" a statistical program for the personal computer.

	ulnar	median	peroneal
DML¶	2.2 mS.	3.0 mS.	4.3 mS.
m-NCV§	60 m/s.	60 m/s.	50 m/s.
CMAP amplitude§†	15.5 mV.	12.3 mV.	6.0 mV.
reduction¶‡	16 %	11 %	41 %
CMAP surface§†	33 mVmS.	29 mVmS.	11 mVmS.
reduction¶‡	11 %	8 %	34 %
CMAP duration¶†	8.1 mS.	7.2 mS.	6.7 mS.
increase¶‡	12 %	12 %	19 %
F-latency¶†	32.3	31.2	59.6

Reference values:
Upper limits¶ and lower limits§ based on 5th, respectively 95th percentile values. † after distal stimulation; ‡ in the trajectory of forearm respectively lower leg. DML and m-NCVs were transformed to a standard temperature of 35° Celsius according to DeJesus, 1973 and Geerlings and Mechelse, 1985.

Curriculum vitae

De schrijver van dit proefschrift werd geboren op 3 mei 1949 te Schiedam. Hij bezocht de Rijks HBS te Schiedam, waar in 1968 het diploma HBS-b werd behaald. Hierna studeerde hij geneeskunde aan de Rijks Universiteit te Leiden, waar hij in 1976 tot arts werd bevorderd. Hierna vervulde hij de militaire dienstplicht bij de Koninklijke Luchtmacht in Blomberg (BRD). In deze periode was hij tevens huisarts in Rinteln (BRD). Vanaf 1 januari 1978 was hij in opleiding tot neuroloog in het Ziekenhuis "De Goddelijke Voorzienigheid" te Sittard (opleider Dr. J.J. Korten), waar hij ook een jaar opleiding in de psychiatrie volgde in de PAAZ (opleider Drs. J.Th.M. Dewez). Als aanvulling op de opleiding neurologie in de periferie volgde hij een jaar opleiding algemene neurologie aan de Katholieke Universiteit van Nijmegen (opleider Prof. Dr. B.P.M. Schulte). In 1982 werd hij ingeschreven als neuroloog in het specialisten register. Hierna volgde de opleiding Klinische Neurofysiologie in het "De Wever" Ziekenhuis te Heerlen (opleider Prof. Dr. J.M.F. Mol). Achtereenvolgens werkte de auteur als neuroloog in het "St. Barbara" Ziekenhuis te Geleen en als klinisch neurofysioloog in het Academisch Ziekenhuis "Annadal" te Maastricht. Sedert april 1985 is de auteur als staflid neurologie verbonden aan het Academisch Ziekenhuis Dijkzigt en het Sophia Kinderziekenhuis te Rotterdam. Sedert 1 oktober 1993 is hij opleider in de Klinische Neurofysiologie en tevens hoofd Klinische Neurofysiologie van het Academisch Ziekenhuis Rotterdam.