Dynamic Changes in the Peripheral and the Central Nervous Systems in Patients with Prior Polio

BY

ARNE SANDBERG
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Abstract

After the acute spell of poliomyelitis, patients commonly suffers from sequelae of weakness. Some of these patients experience new weakness after a time period of stable symptoms.

The aim of this thesis was to evaluate the possible mechanisms for persistent weakness and development of new weakness in prior polio patients.

The usefulness of neurophysiologic methods to study prior polio was evaluated. Also two follow up investigations were performed in the attempt to investigate a possible relationship between development of weakness over time and possible failure in neuromuscular function and relation to muscular activity. In another investigation an evaluation of the exceptional finding of a history of paralytic poliomyelitis without neurophysiologic signs of anterior horn cell death was made. The last investigation dealt with reflex pattern in prior polio and it’s relation to weakness and anterior horn cell loss.

The weakness in prior polio is mainly due to loss of motor neurons with incomplete compensatory mechanisms of reinnervation. The new weakness is mainly due to exaggerated physiological age dependent loss of whole motor neurons, but also fragmentation of the motor unit is likely when these have reached an upper size. Defective neuromuscular transmission and failure in the central drive contribute to a lesser degree to weakness.

Neurophysiologic method of choice for the assessment of motor unit size and the micro-physiology of the motor unit is Macro EMG.

Muscular overuse may accelerate motor unit loss over time in prior polio. Extremely large motor units measured with Macro EMG predict new weakness and Macro EMG can be used for prognostication of development of new weakness in prior polio.

Keywords: polio, prior polio, weakness, Macro EMG, EMG, post polio syndrome

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To Ewa, Martin and Oskar
The thesis is based upon the following papers, which will be referred to in the text by their Roman numerals (I-V):


V **A. Sandberg**, E. Stålberg, Reflexes in prior polio; changed excitability in motorneuron pool. Submitted.


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<td>Agonistic activation</td>
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<td>AHC, AHCs</td>
<td>Anterior horn cell(s)</td>
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<td>Ampl</td>
<td>Amplitude</td>
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<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>ATPase</td>
<td>Adenosine-triphosphatase</td>
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<td>BB</td>
<td>Biceps brachii</td>
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<td>CMAP</td>
<td>Compound muscle action potential</td>
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<td>CNEMG</td>
<td>Concentric needle electromyography</td>
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<td>CS</td>
<td>Citrate synthetase</td>
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<td>CTS</td>
<td>Carpal tunnel syndrome</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>FD</td>
<td>Fiber density</td>
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<td>GBS</td>
<td>Guillain-Barré syndrome</td>
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<td>GM</td>
<td>Gastrocnemius medialis</td>
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<td>H/M-ratio</td>
<td>H-max/M-max ratio</td>
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<td>H-M latency</td>
<td>H-reflex latency minus CMAP latency</td>
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<td>H-max</td>
<td>H-reflex maximal amplitude</td>
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<td>HMSN</td>
<td>Hereditary motor sensory neuropathy</td>
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<td>IGF-I</td>
<td>Insulin growth factor-I</td>
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<td>ILR</td>
<td>Inter limb reflex</td>
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<td>JM</td>
<td>Jendrassic maneuver</td>
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<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<td>M-max</td>
<td>Maximal compound muscle action potential</td>
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<td>MND</td>
<td>Motorneuron disease</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>MU, MUs</td>
<td>Motor unit(s)</td>
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<td>MUNE</td>
<td>Motor unit number estimation</td>
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<td>Post polio muscular dysfunction</td>
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<td>PPS</td>
<td>Post polio syndrome</td>
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<td>Rel</td>
<td>Relative</td>
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<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>SD</td>
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<td>SFEMG</td>
<td>Single fiber electromyography</td>
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<td>SMA</td>
<td>Spinal muscle atrophy</td>
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<td>TA</td>
<td>Tibial anterior</td>
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<td>VL</td>
<td>Vastus lateralis</td>
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Introduction

Epidemics of polio caused large problems for patients and health systems until vaccinations became available in the late nineteen hundred fifties. At that point the epidemics in the western word declined and disappeared to virtual extinction.

However, today polio still exists in third world countries. The number of countries with endemic polio decreased from 125 in 1988 to 6 in 2003 and the number of reported poliomyelitis cases was 682 in 2003 (Centers for disease control and prevention (CDC) 2004).

In the western world, polio-like syndromes now occur. One example of these syndromes is the West Nile virus infection for which there is no vaccine available yet (Eckels & Putnak 2003).

Today polio survivors are coming to health systems for new or accentuated signs and symptoms, particularly weakness, fatigue and pain (Gawne & Halstead 1995; Jubelt & Agre 2000).

The focus of this thesis is on the pathophysiology of weakness in prior polio.
Background

Acute poliomyelitis

History and epidemiology
The first described epidemics of acute poliomyelitis occurred in Norway in 1868 and in Sweden in 1880 and 1887 (Bergenholz 1914). Before that time sporadic cases had been reported. During a 20 year time period (1936-1956) 40,800 polio cases were reported in Sweden, 58 percent of which revealed paralytic polio (Böttiger et al. 1996). For comparison, 25,000-50,000 cases were reported annually in the United States before 1956 (Mulder 1995). The incidence of poliomyelitis dropped dramatically after vaccination campaigns started in the western world in the late nineteen hundred fifties (Gawne & Halstead 1995).

Pathophysiology and clinical picture
Poliomyelitis is commonly caused by an infection of one of 3 types of the polio virus: type1 (Brunhilde), type 2 (Lansing) and type 3 (Leon) of which type 1 caused approximately 85 percent of paralytic cases and most of the epidemics (Dalakas & Hallett 1988). Human infections usually result from person-to-person transmission by fecal-oral contamination (Ranta et al. 2001). There are also other viruses, commonly from the enterovirus group, which can cause clinical poliomyelitis. Recently, the West Nile virus from the Flavivirus group has been reported to cause clinical poliomyelitis (Li et al. 2003; Johnson & Cornblath 2003; Leis et al. 2003).

The infection can also be divided into different groups of successively greater severity: subclinical infectious and abortive poliomyelitis (also called minor illness), and in major illness, comprising non-paralytic poliomyelitis (meningitis) and paralytic poliomyelitis (spinal and/or brain-steam (encephalitic) form). Of those infected, 1-5 percent develop non-paralytic and 1-2 percent develop paralytic poliomyelitis (Gawne & Halstead 1995). The symptoms in the minor illness are dominated by fever, malaise, sore throat and mild gastrointestinal upset. Two to approximately 10 days after the initial symptoms, new symptoms of aseptic meningitis with headache, neck stiffness, irritability, vomiting, fever and drowsiness appear in approximately one quarter of those suffering from minor illness, which then signifies the major illness. Some of the patients affected by major illness
show rapidly developing weakness and paralysis, usually with an asymmetrical distribution in the legs which are commonly more involved than the arms (Sharrard 1955; Mulder 1995). The involvement of brainstem nuclei (reported in about 15 percent of paralytic cases) gives bulbar symptoms. Furthermore, this involvement could give rise to respiratory problems in addition to those produced by the involvement of the respiratory motorneurons. Autonomic and sensory disturbances have been reported, the latter due to a diffuse myelopathy or involvement of dorsal root ganglion cells (Plum 1956).

The pathology was first described as early as 1907 (Wickman 1907). Bodian has described the histopathologic changes in various parts of the central nervous system both in patients and experimental polio (Bodian 1949b; Bodian 1987). If the virus is transmitted from the alimentary tract, there may be dissemination to many regions of the central nervous system, even if clinical symptoms are not necessarily produced despite neuronal and inflammatory changes (Bodian 1949b). Bodian stated that in addition to involvement of the anterior horn cells (AHCs), every case of poliomyelitis exhibits lesions of the brain, with involvement of the intermediate, intermedio-lateral and posterior horns in the spine. Dorsal root ganglia and cerebellum as well as the medulla, pons and midbrain structures were reported involved, showing histopathologic changes and signs of inflammation.

**Diagnosis and differential diagnosis**

The diagnosis is clinical and involves virus isolation and neurophysiological examinations. Nowadays, acute and convalescent titers of serum antibodies to the polio viruses can also be determined. Furthermore, it is possible to determine if a polio virus strain is wild or related to oral vaccine strains (Sabin) (Van Wezel & Hazendonk 1979).

A number of clinical conditions with symptoms such as paralysis, pain, tenderness and immobility in addition to malaise and fever may sometimes cause diagnostic problems. Guillain-Barré syndrome (GBS), acute chemical poisoning, acute porphyria, botulinum infection, tick paralysis and acute transverse myelitis could sometimes imitate the clinical picture of acute poliomyelitis. The bulbar form of poliomyelitis could be similar to Miller Fisher syndrome or myasthenia gravis. However, laboratory investigations can help to differentiate these diseases from poliomyelitis.
Neurophysiology

Electromyography (EMG)
In an early report, fasciculations were found in the pre-paralytic stage of poliomyelitis (Bendz 1952). The first sign of involvement of the AHCs could be reduced recruitment of motor units (Dalakas & Hallett 1988). After 2-4 weeks, fibrillation and positive sharp waves were recognizable as a sign of denervation (Trojan et al. 1991). Usually, polyphasia was present early.

Nerve conduction studies
In the acute stage of poliomyelitis the finding in weak muscles of reduced compound muscle action potentials (CMAP) has been reported (Hari Bhaskar et al. 1997; Jones, Jr. & Darras 2000). Additionally, in some reports the motor conduction velocity was reported to be slightly reduced (Hodes et al. 1947; Hodes 1949). However, in other reports there was a normal motor conduction velocity (Hari Bhaskar et al. 1997; Jones, Jr. & Darras 2000). The sensory neurography was normal.

Recovery and stationary phase

Clinical picture
The clinical recovery from poliomyelitis begins within weeks from the onset of the disease and reaches a plateau after 6-8 months (Gawne & Halstead 1995) and achieves a maximum within the first year (Vallbona et al. 1969). Strength increases in an asymptotic way, with an initial fast phase and subsequently slower improvement (Vallbona et al. 1969). Approximately one third of polio patients show some degree of permanent weakness (Gooch 2002), while others show no signs of permanent weakness despite AHC loss (Luciano et al. 1996). After the first year following the acute phase of poliomyelitis the majority of patients show a stable clinical condition for many years (Halstead & Rossi 1985; Agre et al. 1989).

Pathophysiology
The magnitude of functional recovery is dependent on the number of motoneurons that recover and regain function, effectiveness of collateral reinnervation and degree of muscle hypertrophy (Gawne & Halstead 1995). In a study on animals, only 3-10 percent of AHC showed normal morphology in the acute stage. These changes were reversible in the majority of the motoneuron population (Bodian 1987). Additionally, a recovery of the encephalitis gives rise to functional recovery.
Neurophysiology and muscle biopsy

In the initial recovery phase there are still fibrillation potentials present, as well as polyphasia and reduced interference pattern in the EMG (Bendz 1952; Trojan et al. 1991). When collateral reinnervation has started, there is an amplitude increase proportional to the number of muscle fibers reinnervated. The presence of fibrillation potentials usually diminishes after 6-12 months (Hakelius & Stålberg 1974; Trojan et al. 1991), but in some muscles they are present long after the acute phase (Wiechers & Hubbell 1981; Trojan et al. 1991). In addition to jitter and impulse blocking, single fiber electromyography (SFEMG) shows increased fiber density (FD) (Trojan et al. 1991; Stålberg & Trontelj 1994). Macro EMG shows increased amplitude due to reinnervation (Stålberg 1980; Stålberg 1990) and a possible muscle fiber hypertrophy (Einarsson et al. 1990).

When reinnervation by collateral sprouting takes place, the muscle biopsy reveals an alteration in the normal mosaic interspersion of type I and type II fibers. Fiber type grouping occurs and muscle fiber transition takes place as a result of the influence of the “reinnervating” motorneuron (Kugelberg et al. 1970). Finally, muscle fiber hypertrophy due to weakness and increased activity have been observed (Borg et al. 1988a; Aniansson et al. 1992).

Weakness in the stationary phase

Possible mechanisms for weakness in the stationary phase of poliomyelitis, from peripheral to central anatomical site:

- Alteration of the muscle fiber level
- Failure in neuromuscular (NM) transmission
- Loss of motorneurons
- AHC dysfunction without degeneration
- Changed AHC excitability
- Alteration at spinal or supra spinal level

Possible alterations of the muscle level could be investigated with morphometrical measurements and measurements of contractile properties, in addition to capillarization and chemistry. The two latter factors are mostly discussed in fatigue studies but the numbers of reports on these issues during the stationary phase are still limited. One report concerns “stable” dorsiflexor muscle weakness in prior polio or L5 root showing type I dominance with fiber hypertrophy (Tollbäck 1995). Tollbäck found indications that the contractile properties of “overused” muscle fibers do not change in parallel with the histochemically characterized fiber type. Furthermore, there was an increased maximum shortening velocity in excessively used type I fibers. It was concluded that there is a motor unit
adaptation towards a uniform fiber type with intermediate properties where strength is benefited at the cost of endurance.

Motor unit (MU) loss has shown a relationship to weakness (Tollbäck 1995). With a moderate loss of neurons in the acute stage of poliomyelitis, strength can be fully regained (Sharrard 1953), which is probably due to a practically complete compensation through collateral sprouting and muscle hypertrophy. If the collateral sprouting is incomplete, muscular atrophy and corresponding weakness will occur.

AHC dysfunction without degeneration is another possible mechanism for weakness in poliomyelitis. Bodian has shown that reversible changes may effect the majority of a motorneuron population in the acute stage (Bodian 1987); however, it remains unknown whether this results in remaining dysfunction.

Changed AHC excitability (Soliven & Maselli 1992) in addition to reduced reflex excitability in the motorneuron pool (Prakash et al. 1995; Hari Bhaskar et al. 1997) has been discussed in relation to weakness. Soliven and Maselli found an increased variation in the synaptic delay of the AHCs as a sign of changed AHC excitability, which could be due to altered intrinsic electrophysiological properties of motorneurons or to abnormal temporal and spatial summation of synaptic inputs on motorneurons. Prakash et al and Hari Bhaskar et al used the technique of H-reflex and found decreased responses in children up to 12 months after the acute phase of poliomyelitis. The decreased H-reflex was associated with the degree of involvement of the limb and thus was associated with weakness.

Alteration of a more central level has been discussed primarily as a cause of fatigue (Bruno et al. 1991), but this could also be a cause of persistent weakness, e.g. when the motor area is involved.

Fatigue in the stationary phase
Fatigue is frequently reported in stable poliomyelitis (Agre & Rodriquez 1990; Agre et al. 1998).
Possible mechanisms for fatigue in the stationary phase of prior polio are not analyzed in detail in this thesis. However, it should be mentioned that a study in stable prior polio, dealing with chronically overused MUs showed a slower rate of ATP re-synthesis than consumption, resulting in a possible decreased resistance to fatigue (Grimby et al. 1996). Neither insufficient motorneuron activation nor peripheral blocking played a major role in the loss of force during prolonged muscle contraction.
New symptoms and post polio syndrome

History and epidemiology

The first documentation regarding new symptoms after poliomyelitis were four separate case histories in 1875 (Carriere 1875; Raymond 1875; Cornil & Lepine 1875). Since these initial studies, there have been numerous reports concerning new symptoms in prior polio. For overview see Dalakas and Hallet (Dalakas & Hallett 1988) and Gawne and Halstead (Gawne & Halstead 1995).

Today there are between 10,000 and 16,500 polio survivors in Sweden (Kling et al. 2000). Corresponding numbers in the United States are estimated between 600,000 and 1,600,000 (Jubelt & Drucker 1993; Gawne & Halstead 1995). Assessment of the prevalence of new symptoms among polio survivors shows different numbers in different material, but values up to 80 percent is not uncommon. The prevalence of post polio syndrome (PPS) (for definition see below) was 28.5 percent in one study concerning paralytic poliomyelitis (Ramlow et al. 1992).

Clinical picture

The most common new problems in patients with prior polio are weakness, fatigue and pain, all with prevalence numbers of approximately 50-80 percent in three large investigations (Halstead & Rossi 1985; Agre et al. 1989; Lönnberg 1993). The pain could be subdivided into muscular or joint pain (Willen & Grimby 1998; Vasiliadis et al. 2002) and the fatigue into central, general or muscular fatigue (Gawne & Halstead 1995). Also respiratory disturbances, swallowing difficulties, cold intolerance, muscle tenderness, mastication and voice disturbances are reported (Cosgrove & Alexander 1987; Sonies & Dalakas 1995; Weinberg et al. 1999; Jubelt & Agre 2000; Abaza et al. 2001). Signs of involvement of the autonomic nervous system has been debated (Borg et al. 1988b; Ten Harkel et al. 1991). Symptoms differed between patients and were dependent on the initial involvement (Trojan et al. 1994). The clinical picture presented in a Swedish patient study was similar to that presented in an American patient study (Agre et al. 1995).

Criteria for PPS

There have been several proposals for the terminology and diagnostic criteria regarding the late effects of poliomyelitis. Progressive post poliomyelitis muscular atrophy (PPMA) (Dalakas et al. 1986) and post polio muscular dysfunction (PPMD) (Borg 1996) have been used when the NM symptoms have been in focus. However, the term PPS has gained the widest acceptance as a term for a combination of new symptoms in status post...
polio. The most accepted definition of PPS is the following (Gawne & Halstead 1995):

- History of poliomyelitis
- Characteristic EMG changes
- Improvement after the acute phase
- Stationary phase
- New neurogenic weakness with or without fatigue, atrophy, pain, cold intolerance or decreased function
- No other cause of symptoms

In this thesis this definition of the PPS is used.

Predictive factors for PPS
There are some predictive factors for PPS. Greater weakness during acute poliomyelitis and a longer time since acute poliomyelitis are risk factors for PPS, as well as present muscle or joint pain and recent weight gain (Trojan et al. 1994). The NM symptoms are also associated with a more widely spread acute paralysis, which has a greater functional recovery (Klingman et al. 1988). Additionally, more severe initial poliomyelitis involvement is associated with more pronounced NM symptoms (Agre & Rodriquez 1990).

Possible pathophysiology for new weakness
There is no consensus on the pathophysiology of new weakness in prior polio patients. The different possible levels for dysfunction, i.e. muscular, NM transmission, motorneuron and more central structures, have been discussed relative to possible mechanisms for the new weakness:

- Persistent polio virus infection
- Immune-mediated: inflammation on the spinal level
- Drop-out of motorneurons due to normal aging
- Premature attrition or drop-out of motorneurons due to:
  - neuronal damage from initial infection
  - increased metabolic demand in large MUs or overuse
- Progressive drop-out of muscle fibers due to:
  - Fragmentation of MUs without reinnervation due to normal aging or to increased metabolic demand on the neurons
  - Loss of whole MUs without reinnervation due to above
- Overuse weakness due to transition in contractile properties and firing frequency
- Disuse atrophy
- Weight gain
- Combined effects of muscle overuse, disuse, weight gain or other factors
The persistent polio virus infection has been discussed. Intrathecal Ig-M antibodies to polio virus have been found as a sign of a persistent virus (Sharief et al. 1991) and enterovirus RNA have been detected (Muir et al. 1995; Julien et al. 1999). However, another study failed to show signs of a persistent viral infection (Salazar-Grueso et al. 1989); Thus, the “persistent virus” theory is still a matter of controversy.

The theory concerning inflammation on the spinal level has been evaluated in a histopathological study where signs of inflammation were present in the spinal cord of patients with prior poliomyelitis who died from causes other than polio (Pezeshkpour & Dalakas 1987). Many studies supporting increased inflammatory responses have been performed. A recent study confirmed cytokine production in the central nervous system which was interpreted as a possible inflammatory reaction in patients with PPS (Gonzalez et al. 2002). Nevertheless, the clinical connection and relevance of inflammation and prior poliomyelitis is under debate (Dalakas 2002).

Drop-out of motorneurons is prominent in healthy individuals after 60 years of age (Tomlinson & Irving D 1977; Stålberg & Fawcett 1982; Stålberg et al. 1989; Galea 1996). Trojan has shown that time is a predictive factor for PPS, i.e. the time from the acute polio episode (Trojan et al. 1994). Drop-out of motorneurons with aging alone or in conjunction with another factor has been discussed in the development of PPS (Jubelt & Cashman 1987).

The drop-out of neurons due to persistent neural damage from the initial polio infection (Mulder et al. 1972) or due to excessive metabolic demand (McComas et al. 1973; Dalakas & Hallett 1988) could result in incomplete reinnervation.

Furthermore, the loss of muscle fibers could also be a result of fragmentation of reinnervated MUs (Wiechers & Hubbell 1981; Dalakas & Hallett 1988; Ryniewicz et al. 1990; Emeryk et al. 1990; Pachter & Eberstein 1991; Emeryk-Szajewska et al. 2003) or a mixed pattern (McComas et al. 1997).

Change in the intrinsic properties, i.e. transition from type II to type I fibers have been discussed as a cause for weakness in overused muscles (Borg et al. 1988a). This transition was not due to a selective loss of the high threshold type II MUs (Borg et al. 1979). Larsson et al. (Larsson et al. 1995) found changed contractile properties and increased maximum velocity of unloaded shortening in type I fibers in overused MUs in prior polio patients. These changes were due to overuse and an altered motorneuron firing pattern in chronic use. Larsson et al. found the maximum force per fiber area was low, related to different diffusion distances between small and large muscle fibers in a setup with skinned muscle fibers.

Additional factors, such as weight gain or secondary muscular disuse, caused by either pain inhibition, deconditioning by inactivity (Agre et al. 1991) or altered neural activation pattern could be of importance. In some
patients there is a combination of these factors which multiplies the effect of any single factor (Gawne & Halstead 1995).

Low levels of insulin growth factor-I (IGF-I) were reported to play a contributory role in the pathogenesis of PPS (Shetty et al. 1991) and to correlate with the dysfunction of activities of daily living (Rao et al. 1993). However, an inverse correlation between IGF-I and strength was shown by others (Trojan et al. 2001). Furthermore, Sunnerhagen et al. (Sunnerhagen et al. 1995) showed no correlation between IGF-I and the need for ambulation aids or presence of new symptoms. They concluded that the results did not indicate that IGF-I substitution should be beneficial for prior polio patients.

In a cohort of 50 paralytic polio patients, the new symptoms were not due to a deterioration of NM function (Windebank et al. 1991; Windebank et al. 1995; Windebank et al. 1996) and were unrelated to earlier poliomyelitis, but could be explained by an underlying mechanical disorder.

New fatigue

Fatigue is an ambiguous term that could be separated into emotional, general and muscular fatigue. General fatigue may be a result of cardiovascular deconditioning (Stibrant-Sunnerhagen & Grimby 2001) and muscular fatigue is characterized by the failure to maintain the required or expected force (Edwards 1981).

The muscular fatigue (which have been in some focus in this study) could be divided into central or peripheral fatigue. Central fatigue is due to a reduced central drive of MUs or reduced number of functioning MUs due to malfunction of centrally located nerve cells or inhibition of voluntary effort. Peripheral fatigue may occur from defects of NM junction or defects on the muscular level (Stibrant-Sunnerhagen & Grimby 2001).

The pathophysiology for the new symptom of fatigue has been discussed extensively in prior polio. Examples of the origination for different levels are discussed below.

At the muscle level, muscle enzymes and capillarization have shown deviations which might be important factors for the development of fatigue (Borg & Henriksson 1991). Furthermore, there have been diverse reports regarding energy rich phosphates. Sharma and Kent-Braun reported no difference in energy rich phosphates compared with controls (Sharma & Kent-Braun 1994). It was concluded that the fatigue and delayed recovery of force “must lie beyond the muscle membrane, at the level of excitation-contraction coupling” (Sharma & Kent-Braun 1994). Another report (Nordgren et al. 1997) revealed a decreased level of an energy rich phosphate in prior polio patients, but no differences were detected between the levels in patients with new symptoms and patients with stable symptoms.

NM transmission level has been investigated. Trojan et al (Trojan et al. 1993) showed a defect in the NM transmission in prior polio, but there was
no association between a “fatigue index” and the high frequency disturbance of the NM transmission. Additionally, Maselli et al found a correlation between MU size and disturbance in NM transmission; however, the disturbance in NM transmission was not predictable for the new fatigue (or weakness) (Maselli et al. 1992).

A follow-up investigation assessing muscle performance using twitch interpolation showed no deterioration in muscle endurance over 2.5 years (Allen et al. 1997). The result “supports the view that the symptoms of PPS are not due to a progressive neuronal dysfunction”.

More central causes have been discussed based on lesions in the reticular formation earlier by Bodian (Bodian 1949a) and later by Bruno (Bruno et al. 1995).
General aim of the study

There are two particular reasons for medical interest in this condition, which include the existence of acute poliomyelitis or polio-like illnesses today and the group of patients with prior polio, now showing new or progressive symptoms.

Management and prevention of deterioration of muscular function depend on the thorough understanding of the conditions characterizing status post polio.

Numerous investigations have been performed on these patients in an attempt to explain their existing weakness, new weakness and fatigue.

The aim of this study is to answer the two questions: why is the prior polio patient weak and what are the possible mechanisms for the development of new weakness.

Specific aims in the separate investigations

Investigation I
The aim of the study was to evaluate EMG methods for the assessment of the degree of reinnervation and size of the MU.

Conventional concentric EMG and Macro EMG were compared and the results were further elucidated by means of simulation studies.

Investigation II
The aim of the study was to identify the reason for weakness in prior polio and to investigate the effectiveness and upper limits of the compensatory processes, i.e. reinnervation and muscle fiber hypertrophy. It was also intended to further elucidate a possible relationship between symptoms, the decrease in muscle strength and the compensatory processes.

The study included an assessment of NM junction, EMG parameters of reinnervation, biopsy, force and dynamic changes of some of these parameters over time.
Investigation III
The aim of this study was to evaluate the exceptional findings of patients with an alleged history of paralytic poliomyelitis and the appearance of new symptoms, but normal neurophysiology. Possible explanations for this combination were discussed.

Investigation IV
The aim of this study was to study the importance of muscular activity in a limb muscle over time in the development of new weakness in relation to AHC loss.
   One arm and one leg muscle were compared.

Investigation V
The aim of the study was to evaluate the reflex pattern in patients with a history of polio and to relate these findings to the degree of neurogenic changes and muscle force.
Material

Investigation I

One hundred twenty-one patients with prior polio referred from various centers of rehabilitation and neurology to the Department of Clinical Neurophysiology for EMG investigations were included retrospectively.

There were inclusion criteria of a history of acute polio more than 20 years ago and no other major neurological disorders. The exclusion criteria were concomitant disorders that would have an impact on the results. Two patients were excluded, one patient suffering from L5 radiculopathy and one patient with hereditary motor sensory neuropathy type 1 (HMSN 1). The inclusion criteria for separate muscles were that quantitative analysis had been made with data from at least 15 motor unit potentials (MUPs) with both Macro EMG and concentric needle EMG (CNEMG) from at least one of the following muscles: biceps brachii (BB), vastus lateralis (VL) or the tibialis anterior (TA). Results from each muscle were treated separately.

All patients gave their informed consent and the study was accepted by the ethics committee of the hospital.

Patient data from investigation I is summarized in Table 1.

<table>
<thead>
<tr>
<th>No. muscles</th>
<th>Age (mean ± SD)</th>
<th>Time since polio (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>63</td>
<td>62.9 (9.0)</td>
</tr>
<tr>
<td>VL</td>
<td>93</td>
<td>57.2 (10.7)</td>
</tr>
<tr>
<td>TA</td>
<td>105</td>
<td>57.8 (11.2)</td>
</tr>
</tbody>
</table>

Table 1. Summary of patient material in investigation I.

BB= biceps brachii muscle, VL= vastus lateralis muscle and TA= tibialis anterior muscle. (From investigation I, © Elsevier)
Investigation II

For investigation II, 30 legs in 21 prior polio patients (10 men and 11 women, aged 48 ± 2 years, range 40-65 years at the first examination) with sequelae of poliomyelitis were followed over an 8-year period at three occasions (i.e. 0, 4 and 8 years).

Inclusion criteria were a history of paralytic poliomyelitis and the investigated legs had to have been clinically affected in the acute phase of poliomyelitis. The muscle strength in knee extension had to show an ability to resist gravity. Exclusion criteria were the presence of any medical condition that may have an impact on the results.

Muscle strength was measured on three occasions in all legs with the ability to resist gravity for knee extension. EMG was performed at the three occasions in 26 legs in 17 polio patients and muscle biopsies were taken in 10 legs in 9 patients.

The polio patients had acute polio approximately 38 ± 1 (range 24-51) years before the first examination. At the onset of poliomyelitis they were 11 ± 2 (range 1-33) years old. At the first examination, 12 patents fulfilled the criteria of PPS stated by Halstead and Rossi (Halstead & Rossi 1985). Eighteen patients fulfilled the criteria at the second examination and 20 at the final examination.

The term “stable” (no new or increased muscle weakness) and “unstable” (increased symptomatic muscle weakness) legs were used as suggested by Gawne and Halstead (Gawne & Halstead 1995). Ten of the legs were characterized as stable and 20 as unstable, as determined at the final examination. Of the 10 legs in which muscle biopsies were performed the corresponding figures were 1 stable and 9 unstable. In the legs with EMG recording from the 17 patients, 10 were stable and 16 unstable.

No patients reported any new illness or medical condition to explain the new muscular symptoms. Walking aids were used by 52 percent of the patients. Informed consent was given by all patients. The procedures were approved by the ethics committee.

Investigation III

Thirty-five patients with negative neurophysiologic findings were found in a total material of 688 patients with a history of polio from the Uppsala laboratory from 1989 to 2001. Patients were referred from various centers of medical rehabilitation and neurology. The material was not considered to represent the general population of polio patients. Patients with negative neurophysiologic findings were retrospectively selected for the study according to specified criteria.
Inclusion criteria: Patients who presented progressive or new symptoms with normal neurophysiological findings and had a previous clinical diagnosis of “paralytic polio” (verified or strongly suspected) were included. The investigation had to include the limb with old or new symptoms, including the muscles in which there may have been an involvement according to reported functional loss. Patients with a slightly abnormal EMG were also included if there was a reason other than polio for the findings.

Exclusion criteria: A case was not included if the diagnosis was very uncertain or if the neurophysiological investigation was incomplete and did not include the area (limb) showing symptoms. A judgment was made that the negative neurophysiological finding was not due to poor quality of data.

Eight patients were excluded.

Thirty-five patients remained after inclusion and exclusion criteria had been taken into consideration. Special attention was paid to the reliability of the original diagnosis; however, in most cases the diagnosis was difficult to establish with objective means. The present late assessment of the diagnosis was based on scrutinizing patient files (available in 28 cases), contacting the referring physicians and recording the history given by each patient. The material collected was divided into 5 groups:

1. **Another diagnosis.** The patient had a diagnosis of polio sequelae until the present EMG and further retrospective studies reached a different diagnosis.
2. **Uncertain diagnosis.** The patient was not hospitalized and had no defined acute spell of symptoms.
3. **Polio meningitis.** Symptoms of meningitis dominated the acute stage.
4. **Suspected history of paralytic polio.** The patient had acute symptoms, with or without hospitalization.
5. **Paralytic polio.** The patient had definite weakness, usually for months, and recovered slowly. No other reason for the clinical condition was revealed.

The study was accepted by the local ethics committee.
Investigation IV

In investigation IV both a test-retest study of Macro EMG and a follow-up study of Macro EMG were performed.

Test-retest study:
To examine the reproducibility of Macro EMG, a test-retest of Macro EMG was made in the TA muscle of both healthy controls and prior polio patients. Fourteen TA muscles of 14 healthy control subjects (8 men, 6 women) were studied at 2 investigations performed 1 month apart. We tested 20 TA muscles in 19 post polio patients (9 men, 10 women who were not included in the follow-up study described below) at 2 separate investigations during the same day. The control subjects were 37.9 ± 10.6 years old and the patients 62.2 ± 10.1 years old. One investigator performed all test-retest studies.

Follow-up study:
The patient group consisted of 23 prior polio patients in whom 28 of each TA and BB muscles were studied. Patients with a clinical diagnosis and neurophysiologic findings compatible with prior polio were included, independent of the degree of polio involvement in the 2 muscles (i.e., 1 of 2 muscles could be normal). To be included in the study, each patient had to have at least 1 TA and 1 BB muscle in sufficiently good condition for a quantitative study and at least 10 acceptable Macro MUPs, as determined by EMG. In some patients, studies were performed bilaterally. Each patient was seen by 1 of 2 investigators (the authors) in the study after on average 5.6 years (range, 3.6–7.1). Fourteen patients suffered from PPS. Ten patients (7 with PPS) initially used a cane regularly. All patients were physically active and none used a wheelchair. Exclusion criteria were other neurological disorders that might affect study results.

No patients showed signs of concomitant disorders that may have affected the results.

The study was accepted by the local ethics committee and the patients signed a written consent.
Investigation V

At investigation V reflexes were recorded in both prior polio patients and controls. EMG was only performed in the prior polio patients.

Patient material:
Inclusion criteria was a diagnosis of paralytic polio verified with EMG, the clinical progression regarding new symptoms was not part of the criteria. There was no selection of patients in respect to the degree of involvement of different muscles, with the exception that there should be noticeable symptoms in the legs. Patients were excluded if they had a suspected or confirmed concomitant disorder that could have an impact on the results. Twenty-five patients (11 women and 14 men) were included. The average age was 63.4 years (range 42-78), average age at acute polio was 9.6 years (range 1-29) and the time since acute polio was 55 years (range 40-75). Patients’ height was on average 170 centimeters. Nineteen patients suffered from PPS, with a mean duration of 8 years. One patient had new weakness within the last year.

In general, the symptoms present consisted of different degrees of weakness in 24 patients, fatigue in 17 patients, pain in 19 patients and cold intolerance in one patient. Sixteen of the seventeen patients with fatigue had weakness. Muscle atrophy was present in 20 patients.

Controls:
Twenty controls, 11 woman and 9 men, with a mean height of 171 centimeters and age of 62.9 years (range 40-84), with no sign of neurological or orthopedic disease, were investigated regarding reflexes, including the qualitative assessment of stretch reflexes, electrophysiological recordings of the H-reflex and T-response and reflexes with long latency, such as inter-limb reflexes and the startle response.

This study was accepted by the local ethics committee. All patients and controls gave their informed consent.
Methods

Macro EMG

The standard Macro EMG method was applied (Stålberg 1980) using commercially available Macro EMG needles (Medelec, Oxford instruments, Abingdon, Great Britain, and Medtronic, Copenhagen, Denmark) in all five investigations.

The recording electrode consisted of a modified SFEMG electrode with the cannula insulated with Teflon, except for the distal 15 millimeters. An SFEMG recording surface was exposed 7.5 millimeters from the tip. Recordings were made on two channels of commercially available EMG equipment (Keypoint, Medtronic, Copenhagen, Denmark). For “early” recordings in investigation I, II, III and IV, the Counterpoint (Dantec, Copenhagen, Denmark) was used. On the first channel, the SFEMG activity was displayed (using the cannula as reference) and used to identify the MU and to trigger an averaging procedure. Filter settings were 500 hertz - 10 kilohertz. The FD of the triggering single fiber electrode was recorded. Visual assessment of jitter and blocking were made. On the second channel, the activity from the cannula (using a remote surface electrode as a reference) was averaged until a smooth baseline and a constant Macro MUP were obtained. Filter settings were 5 hertz - 10 kilohertz.

The results from each muscle were expressed as the median value of at least 10 recordings at three needle insertions (except one muscle in investigation I). The area of the Macro MUP during the entire sweep time of 70 milliseconds was also obtained. A simulation study showed that this was an equally good indicator of the size of the MU as amplitude; however, in situations with a small MU the area becomes erroneous and the amplitude is more precise (Nandedkar & Stålberg 1983a). Reference values included the mean of median values of individual amplitudes and upper and lower extreme values of individual Macro MUP amplitude and area for healthy subjects in the age range of 20 to 80 years (Stålberg & Fawcett 1982). Only the amplitude values were reported. The age related value, or relative amplitude, was calculated as the quotient:

\[
\frac{\text{obtained median amplitude}}{\text{mean of median values from age matched controls}}.
\]
Concentric needle EMG

CNEMG was performed at investigations I, III and V.

The standard concentric needle (Medelec, Oxford instruments, Abingdon, Great Britain; Medtronic, Copenhagen, Denmark and Medicotest, Copenhagen, Denmark) consists of a 150 micrometer diameter wire as the active recording element inside a cannula. The tip is ground to a 15 degree angle, producing an elliptical recording surface of the wire (150 x 580 micrometers), which has an area of 0.07 square millimeters. The majority of the EMG recordings were performed on Keypoint EMG equipment (Medtronic, Denmark); however, in the early cases Cantata and Counterpoint (Dantec, Denmark) were used. Analysis of spontaneous activity at rest was assessed visually. MUP analysis was performed automatically with an inbuilt program called Multi MUP analysis (Stålberg et al. 1996) in the recordings performed with the Keypoint, otherwise manual analysis was performed. The Multi MUP analysis is based on signal decomposition and averaging. Manual editing was performed when necessary. Usually 20 different MUPs were obtained. This was typically carried out with 2-3 skin penetrations at 3-5 different recording sites in each penetration. At each recording site, 1-4 different MUPs were obtained.

The results were expressed as mean values of various parameters, Z-scores, relative mean values normalized for age using a large control group and in terms of individual outliers (Bischoff et al. 1994a; Bischoff et al. 1994b). The stability of individual MUPs, the jiggle (Stålberg & Sonoo 1994) and blocking, were assessed visually. The interference pattern at strong voluntary contraction was either assessed with the inbuilt program or scored visually.

EMG score

An EMG score was used in investigation V. An “EMG score” was assessed for the comprehensive EMG findings of a particular muscle. The CNEMG and Macro EMG were scored as follows:

0 = Normal findings.
1 = Slight neurogenic findings. For CNEMG the finding of a slightly increased MUP amplitude and mean amplitude elevation between 2 SD (compared to controls) (Bischoff et al. 1994b) and 4 SD, in addition to polyphasicity and slightly reduced interference pattern, were defined as slight neurogenic findings. For Macro EMG, a median MUP amplitude above 2 SD (approximately a relative amplitude of 1.4-2.5 (Stålberg & Fawcett 1982)) was used as a limit for abnormality and a relative amplitude value below 4 was interpreted as slight involvement. The FD was assessed and a slight
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Elevation (Stålberg & Trontelj 1994) in this parameter was taken as support for reinnervation.

2 = Moderate neurogenic findings. Moderately increased MUP amplitude, +4 to 6 SD in CNEMG, as well as increased duration and moderately reduced interference pattern, were defined as moderate neurogenic. In Macro EMG a relative Macro amplitude between 4 and 6.5 was interpreted as moderately increased.

3 = Pronounced neurogenic findings. Pronounced changes in all of the above stated parameters, more than +6 SD in CNEMG amplitude and a greater relative amplitude than 6.5 in Macro MUP were interpreted as pronounced.

4 = Complete denervation. There were no recognizable MUPs found during all attempts to activate the muscle.

If both CNEMG and Macro EMG were performed (which was the case in some VL muscles), the EMG score was based on the combined findings from both of these techniques.

**Simulation of EMG**

Simulation of CNEMG and Macro EMG were performed in investigation I. Single fiber action potentials were simulated according to the line source model described elsewhere (Nandedkar & Stålberg 1983b). MUs were simulated with various numbers of muscle fibers, ranging from 1 to 100 per square millimeter for the entire MU using a constant MU territory of 6 millimeters in diameter. This MU territory corresponds to a range from sparse to moderately dense fiber packing. The fibers were scattered randomly in the territory. The fiber diameter was in the normal range 55 ± 6 (mean ± SD, range 30-70 micrometers) (Brooke & Engel 1969). Parameters of temporal dispersion of single fiber action potentials and distance dependent amplitudes (Nandedkar et al. 1984) of the single fiber action potentials were included in the model. The shape of the single fiber action potentials were simulated as being recorded with a CNEMG needle. They were summated to generate a MUP as recorded with a concentric needle electrode. The contribution of the cannula was estimated and subtracted to simulate a concentric needle MUP.

Similarly, the SFEMG action potentials were also given a shape obtained from a Macro electrode. The Macro MUP shape was generated by the summation of the SFEMG action potentials, taking into account the physical extent of the electrode according to the model described elsewhere (Nandedkar & Stålberg 1983a). In investigation I, the comparison between the two methods, concentric needle MUPs and Macro MUPs were simulated.
from the same simulated motor unit. The amplitudes of the generated MUPs were measured and correlated to number of activated muscle fibers.

**Neurography**

In investigations III and V neurography was performed, but was confined to F-responses in study V.

Neurography was performed according to the standard used in the Uppsala laboratory, described elsewhere (Stålberg et al. 1999). Surface electrodes were used for stimulation and recording. Commonly, the median, ulnar, peroneal and tibial nerves were investigated. Parameters included CMAP amplitude, area, latency, proximal-distal change in amplitude and duration, F-wave minimal latency minus M-latency and persistence.

Sensory neurography was performed with surface stimulating and recording electrodes. Commonly sural, median and ulnar nerves were investigated. Reference values were from the Uppsala laboratory.

**Reflexes**

**Monosynaptic reflexes**

**Tendon jerk**

The tendon jerk was assessed in investigation V.

The same investigator made a visual assessment of the tendon jerk responses after a tendon tap of the Achilles and patellar tendons using a conventional reflex hammer. Three or more responses were assessed for each stretch reflex, with more than a 10-second pause between the stimulations. For the study of the Achilles reflex, the subject rested prone. For the study of the patellar reflex, the subject sat relaxed in a reclined chair with the knee joint supported at approximately 30 degrees of flexion. The reflexes were assessed as brisk, normal, slightly decreased, moderately decreased, pronounced decreased and absent.

**T-response**

The T-response was assessed in investigation V.

The stretch reflex obtained at the patellar tendon tap (T-response) was recorded with surface EMG electrodes over the VL muscle. The active recording surface electrode was placed at the junction of the middle and distal third of the VL muscle. The reference surface electrode was located just distal to the spina iliaca anterior superior. Mechanical forceful stimulation to the patellar tendon was performed in an attempt to get a
“maximal” amplitude response using a hammer (Dantec type 15 B 01) with an in-built mechanism to trigger the EMG measurement.

The reflex test was performed at rest, during slight muscular agonistic activation (AA) and during the Jendrassic maneuver (JM). Amplitude and onset latency were measured. From each level of activation the response with the highest amplitude was chosen for analysis.

**H-reflex**

The H-reflex was performed in investigation V.

The H-reflex was measured in the triceps surae. The tibial nerve was stimulated with surface electrodes in the patellar fossa with the cathode placed proximal to the anode over the nerve. Stimulus duration was 1 millisecond with at least a 10 second interval between consecutive stimuli. The uptake active electrode was placed over the distal part of the gastrocnemius medialis (GM) muscle and the reference electrode was placed over the distal part of the Achilles tendon, proximal to its insertion into the calcaneus bone.

With increasing stimulus strength, the H-reflex normally increases in amplitude to a certain limit after which it decreases, the CMAP increases in amplitude simultaneously. The H-reflex maximal amplitude (H-max) depends on the effectiveness of Ia afferent stimulation, amount of other peripheral and central facilitation, interneuronal inhibitory neurons and motorneuron excitability (Schieppati 1986; Hilgevoord et al. 1995). For quantification of the H-reflex the maximum CMAP (M-max) was measured and the H-max/M-max quotient was expressed as a percentage (H/M-ratio). Furthermore, the latency of both the H-reflex and M-response were measured.

The H-reflex latency minus M-response latency (H-M latency) was calculated to remove the influence of the distal latency in the analysis.

Monosynaptic reflexes were tested unilaterally in the controls.

**Polysynaptic reflex**

**Inter-limb reflex**

The inter-limb reflex (ILR) was assessed in investigation V.

The ILR is described in detail in decapitated cats (Lloyd & McIntyre 1948), spinal cord injury (Calancie 1991), neurological intact humans (Zehr et al. 2001; Haridas & Zehr 2003) and in prior polio (Ertekin et al. 2002). In ILR, the linkage between the forelimb and the hind limb has been related to posture and locomotion (Lloyd & McIntyre 1948). The ILR system likely exists in humans; however, it has been reported either inactive, rudimentary or of less importance as compared to quadripedal animals (Ertekin et al. 2002).
The ILR was studied using surface electrodes for stimulation and recording. Electrical stimulation of the median and ulnar nerves (ipsi-lateral to the recording side) was performed at the level of the wrist. Stimulation of the plexus brachialis was performed ipsi- and contra-lateral to the recording side. Three levels of stimulus intensity were used, all eliciting a clear, visual motor response in the upper limb without pain sensation. At least 3 stimuli were delivered to each stimulus level and consecutive stimuli were separated by a minimum of 10 seconds. Duration of the single square wave electrical stimuli was 0.2 milliseconds. The response with the shortest latency from each location was further analyzed. ILR recordings were made from the VL muscle.

The criteria to be classified as ILR included a stimulus intensity that did not elicit painful or any otherwise unpleasant sensations (to avoid flexor reflex response). The ILR was obtained with a stimulus strength of 20-50 milliamperes, however up to 90 milliamperes were sometimes necessary to elicit a ILR response. The response was grossly reproducible in shape at the consecutive stimuli and was allowed to show some latency changes at consecutive stimuli without any distinct habituation (Ertekin et al. 2002). The maximum latency for a response still to be considered as ILR has been discussed in the literature (Zehr et al. 2001; Calancie et al. 2002; Ertekin et al. 2002). In investigation V we have accepted responses with latencies in the range of 45-190 milliseconds as ILR, provided they also fulfill the features discussed above.

**Force measurement**

**Muscle strength and endurance**

Muscle strength and endurance were measured in investigation II.

**Isometric, isokinetic force and endurance test**

Knee-extensor strength for isometric contraction at a knee angle of 60 degrees and for isokinetic concentric contractions at angular velocities of 60 and 180 degrees per second were measured using dynamometers.

Measurements were obtained from both lower extremities provided that EMG showed signs indicative of prior polio and that full knee extension against gravity could be performed. Warming-up sub-maximal exercise was performed on a bicycle ergometer for 6 minutes prior to the muscle tests. The torque values were recorded with a computerized system which used compensation for the weight of the lower leg and the lever arm. Three curves were recorded, and the highest peak torque value was reported. Results from randomly selected healthy men and women of ages matching the prior polio subjects were used as control values (Sunnerhagen KS et al. 2000).
During isometric muscle contraction, percutaneous electrical stimulation was given to evaluate the superimposed single-twitch (Rutherford et al. 1986) of the quadriceps muscle. This study was performed at the third examination, i.e. after 8 years. Subjects were instructed to maintain various activation levels by matching their effort with level indicators. Extrapolation from linear regression analyses was made using the additional torque produced by the superimposed twitches as a dependent variable to calculate a theoretical maximal isometric torque.

Endurance was measured as the reduction in peak torque between the first and the last three knee extensions in a series of 50 concentric maximal voluntary contractions with an angle of velocity of 180 degrees per second (Thorstensson & Karlsson 1976). The total time for the test was approximately 1.5 minutes.

**Force testing (MRC scale)**

Force was assessed in investigation V by the same investigator in plantar flexion and knee extension muscle groups. The Medical Research Council (MRC) 0-5 scale was used (Medical Research Council. 1976):

- 0 = No contraction.
- 1 = Flicker or trace of contraction.
- 2 = Active movement, with gravity eliminated.
- 3 = Active movement against gravity.
- 4 = Active movement against gravity and resistance.
- 5 = Normal power.

The force is a contribution from several muscles. It was not possible to test the force produced by separate muscles without an invasive approach.

**Patients’ assessment of symptoms**

The clinical situation was important in all investigations, but a further “scaled” assessment was made in investigations IV and V.

In investigation IV the patients’ assessments of weakness and fatigue at consecutive investigations were evaluated on a 4-point scale (0 = normal, 1 = slight, 2 = moderate and 3 = pronounced symptoms). Assessment of other symptoms, such as pain and cold intolerance, was made on an absent or present basis. A clinical assessment of PPS was made. Devices for increased mobility were noted.

In investigation V the patients’ assessment of weakness in the knee extension was evaluated on a five-point scale (0 normal, -1 slight, -2 moderate, -3 pronounced weakness and -4 complete loss of function).
Muscle biopsy

Muscle biopsies were performed during investigation II. Muscle biopsies were taken with an alligator forceps (Henriksson 1979) under local anesthesia from the middle portion of the VL muscle at the three occasions (0, 4 and 8 years). The biopsies were taken close to each site at the consecutive occasions but avoided identical sites. Two parts of muscle specimen were taken. One part was frozen immediately in liquid nitrogen and used for analysis of enzymatic activities, while the other part was used for histochemical and histopathological analyses.

The myofibrillar adenosine-triphosphatase (ATPase) method was used for muscle fiber classification. Fibers were classified as type I and type II at reactions carried out at pH 9.4 following alkaline preincubation (pH 10.3). The type II fibers were further sub-classified as IIA, IIB and IIC fibers using a preincubation at pH 4.62 and 4.35. The fiber areas were measured on photos of nicotinamide adenine dinucleotide hydride tetrazolium reductase-stained transverse sections. Measurements from oblique muscle fiber sections were avoided. On average, fiber areas were measured as 210 ± 20, 180 ± 25 and 218 ± 25 fibers respectively, at the three occasions. For comparison, results from randomly selected age matched healthy controls were used.

For biochemical assays, the enzyme activity was determined using fluorimetric techniques. The reactions catalyzed by enzymes under investigation were coupled to nicotinamide adenine dinucleotide-nicotinamide adenine dinucleotide hydride linked reactions. Analyses were made for several enzymatic activities, including triphosphonate dehydrogenase, lactate dehydrogenase, myokinase and citrate synthetase (CS). Enzyme activity was expressed per gram of protein.

Amylase-periodic acid Schiff (PAS) staining was used to visualize capillaries. The number of capillaries per fiber and fiber area per capillary were calculated (Grimby et al. 1989).

Statistics

Linear regression analysis was used in investigation I. The Pearson correlation coefficient was used to study the interrelations between parameters. The significance of correlation coefficients was two-tailed tested.

In investigation II the Wilcoxon nonparametric (signed-rank) test was used for paired observations and the Mann-Whitney U-test was used for unpaired observations.

In investigation III there was no need for statistical analysis.
In investigation IV paired- or independent-sample \( t \) tests (2-tailed), in addition to the Wilcoxon signed-rank test were used to compare means. Linear regression analysis, including the Pearson correlation coefficient was used to study correlations between parameters. When ordinal-scaled variables were present, the Spearman correlation coefficient in bivariate correlations or the Fisher’s exact test was used in addition to the Pearson Chi-square test. The calculations of the differences between TA and BB muscles took place if one of each muscle was investigated, they were accepted for comparison; however, in cases where 4 muscles were studied, comparison was made between ipsi-lateral sides and when 3 muscles were studied, only the ipsi-lateral TA and BB were used.

In investigation V, the t-test (parametric variables) for dependent and independent samples, in addition to the Wilcoxon signed rank test and the Mann-Whitney U-test, was used for comparison of means. When more than two mean values were compared, analysis of variance (ANOVA) was used in addition to Friedman test for nonparametric or assumed not normal distributed materials. Linear regression analyses, including Pearson correlation coefficient, were used to study correlation between parameters. When ordinal-scaled variables were present, the Spearman correlation coefficient in bivariate correlation or Fisher’s exact test, in addition to the Pearson Chi-square test, was used.

All statistics for investigations I-V were performed with commercially available software, SPSS (Chicago, IL). Results were considered significant with \( P < 0.05 \).
Results

Investigation I

During investigation I, a comparison between CNEMG and Macro EMG were performed in prior polio patients, in addition to simulation of both EMG techniques.

EMG

Of the three muscles studied (BB, VL and TA) CNEMG showed the most pronounced changes in the VL and the least in the BB. CNEMG was abnormal in 211 out of 261 investigated muscles, while the corresponding number for Macro EMG (including SFEMG) was 246 abnormal of 261 investigated muscles. Macro EMG showed increased amplitudes in 223 out of the 261 investigated muscles. In general, the relative change was more pronounced in Macro EMG. Macro was abnormal more often than CNEMG. In general, the FD was increased when the Macro amplitude was increased; however, in 29 cases the FD was indicated normal when Macro amplitude was elevated, which was presumably due to improper quantitation of FD, but could in some cases be due to fiber hypertrophy, giving high Macro MUPs but normal FD. Table 2 shows the separate results from CNEMG and Macro EMG.

There was a correlation between the changes in CNEMG and Macro EMG (Figure 1). The regression analysis (Table 3) showed a higher coefficient of determination for the regression of Macro amplitude and CNEMG amplitude than Macro amplitude and CNEMG duration for all three muscles.

A summary of the results comparing the final conclusion from CNEMG and Macro EMG is given in Table 4. In the 28 cases with normal CNEMG amplitude but abnormal Macro amplitude, the FD was abnormal in 19 cases, but normal in 9.
Table 2. Results for CNEMG and Macro EMG including FD. For CNEMG “abn EMG (over all)” means that at least one of the MUP parameters amplitude or duration is outside 2 SD of age matched reference values or that the interference pattern at full effort is reduced. For all other parameters, “abn” indicates values outside 2 SD in healthy age matched controls. For Macro EMG, the mean of all relative median values are given. (From investigation I, © Elsevier)

* = because of skew distribution, the values are calculated after log transformation. The values in the table are given after linear transformation of the calculated value.

<table>
<thead>
<tr>
<th></th>
<th>BB</th>
<th>VL</th>
<th>TA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNEMG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># muscles studied</td>
<td>63</td>
<td>93</td>
<td>105</td>
<td>261</td>
</tr>
<tr>
<td># of abn EMG (over all)</td>
<td>37</td>
<td>79</td>
<td>95</td>
<td>211</td>
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<td># of abn EMG ampl</td>
<td>37</td>
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<td>95</td>
<td>210</td>
</tr>
<tr>
<td>rel ampl*; mean, range of 2 SD</td>
<td>2.02</td>
<td>0.58-7.04</td>
<td>3.79</td>
<td>1.06-13.6</td>
</tr>
<tr>
<td># of abn EMG dur</td>
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<td>28</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>rel dur*; mean, range of 2 SD</td>
<td>1.16</td>
<td>0.64-2.07</td>
<td>1.33</td>
<td>0.88-2.02</td>
</tr>
<tr>
<td>Macro EMG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># muscles studied</td>
<td>63</td>
<td>93</td>
<td>105</td>
<td>261</td>
</tr>
<tr>
<td># abn Macro ampl</td>
<td>49</td>
<td>87</td>
<td>87</td>
<td>223</td>
</tr>
<tr>
<td>rel ampl*; mean, range of 2 SD</td>
<td>3.56</td>
<td>0.79-16.0</td>
<td>6.38</td>
<td>1.31-31.0</td>
</tr>
<tr>
<td>FD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># abn (total)</td>
<td>58</td>
<td>72</td>
<td>87</td>
<td>217</td>
</tr>
<tr>
<td># abn FD/ normal Macro MUP ampl</td>
<td>12/14</td>
<td>3/6</td>
<td>8/18</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Plot of relative (rel) CNEMG amplitude (ampl) versus relative (rel) Macro EMG amplitude (ampl) in the VL muscle. The slope of the regression line is 0.274 ($r^2 = 0.40$). The upper normal limits for the two parameters are indicated with hatched lines. Note the higher number of abnormal Macro EMG findings when CNEMG was normal, than the opposite. (From investigation I, © Elsevier)
Table 3. Regression analysis of indicated parameters. Slope and $r^2$ values are given. There is a higher coefficient of determination for the regression of Macro amplitude and CNEMG amplitude than Macro amplitude and CNEMG duration.

Significance: *$P < 0.01$, **$P < 0.001$

a Outliers outside

(Modified from investigation I, © Elsevier)

<table>
<thead>
<tr>
<th></th>
<th>Rel CNEMG ampl slope</th>
<th>$r^2$</th>
<th>Rel CNEMG dur slope</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel Macro ampl BB</td>
<td>0.26**</td>
<td>0.55a</td>
<td>0.029**</td>
<td>0.21a</td>
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<td>Rel Macro ampl VL</td>
<td>0.27**</td>
<td>0.40</td>
<td>0.017**</td>
<td>0.14</td>
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<tr>
<td>Rel Macro ampl TA</td>
<td>0.27**</td>
<td>0.42</td>
<td>0.013*</td>
<td>0.070</td>
</tr>
</tbody>
</table>

Table 4. Summary of findings in CNEMG (amplitude and duration) and Macro EMG. Note the different higher yield of pathology for Macro EMG than for CNEMG and for CNEMG amplitude than for duration.

$n$ = normal, $abn$ = abnormal

(From investigation I, © Elsevier)
Simulation of EMG

Amplitudes of CNEMG and Macro EMG were simulated with various numbers of muscle fibers (Figure 2). The slope for the regression line for the correlation between the CNEMG relative amplitude and the number of fibers was 0.0019 (P < 0.001), \( r^2 = 0.88 \). The slope for the regression line for correlation between Macro relative amplitude and number of muscle fibers was 0.0053 (P < 0.001), \( r^2 = 0.995 \). The slope for the regression line for correlation between CNEMG relative amplitude and Macro relative amplitude was 0.36 (P < 0.001), \( r^2 = 0.88 \); however, this slope is somewhat larger than that obtained in the actual EMG recordings, which was 0.26, 0.27 and 0.27 for BB, VL and TA respectively.

Figure 2. Simulation of EMG. Plot of relative amplitude on the y-axis versus the number of fibers for CNEMG and Macro EMG on the x-axis. The number of fibers continuously increases from 1 to 100 fibers per square millimeter corresponding to a total of 28-2827 fibers within a territory of 6 millimeters in diameter. Only 20 percent of the MUs are shown for the sake of clarity. The regression line for all MUs are shown (full lines). The obtained summated signal increase in amplitude, more so for Macro simulation. Slope for the regression line is 0.0019 (\( r^2 = 0.88 \)) for CNEMG and 0.0053 (\( r^2 = 0.99 \)) for Macro EMG. Note the greater variation in increasing amplitude with the addition of muscle fibers in CNEMG as opposed to Macro EMG simulations. (From investigation I, © Elsevier)
Summary
Macro EMG was abnormal more often than the CNEMG. The simulation supported the finding of a more pronounced relative change in amplitude for Macro EMG than for CNEMG. In addition, there was a higher coefficient of determination for the correlation between Macro amplitude and number of muscle fibers than the correlation between CNEMG amplitude and number of muscle fibers.

To conclude
For quantitative assessment of MU size Macro EMG is superior compared with CNEMG in prior polio.

Investigation II
In investigation II muscle strength, Macro EMG and muscle biopsy were followed at three occasions over 8 years.

Muscle strength and endurance
For the prior polio group (30 legs) there was a decrease in isometric strength of 9 ± 3 percent (P < 0.02) over the 8-year period. The corresponding numbers (both significant) for isokinetic strength were 13 percent at 60 degree per second angle velocity and 15 percent at 180 degrees per second angle velocity. At the last examination the muscle strength values were 61 ± 6 percent for isometric force, 61 ± 5 percent for isokinetic force at 60 degrees per second angle velocity and 63 ± 6 percent for isokinetic force at 180 degrees per second angle velocity compared to controls. When separating the muscles into two groups (one group consisting of those legs with increased weakness over the period (unstable, 20 legs) and another group consisting of legs without increased weakness over the period (stable, 10 legs), the unstable legs showed a significant decrease in strength during the period (isometric 12 ± 4 percent; isokinetic 60 degrees per second, 14 ± 3 percent; isokinetic 180 degrees per second, 19 ± 3 percent). The stable legs showed significant decrease in strength only for the isokinetic measurements at 60 degrees per second (Figure 3). The superimposed single twitch technique was performed at the last examination for isometric measurement. The lack of maximal activity calculated as a percentage of the theoretical maximal value was 5.7 ± 3.1 percent (95 percent confidence interval –0.9 to + 12.2). There was no difference in this parameter between unstable and stable legs.
Figure 3. Peak torque values for isokinetic concentric knee extension at 60 degrees per second at the initial examination and after 8 years. The decrease in strength was significant both for the stable and the unstable legs over the period. (From investigation II, © Wiley)

The endurance test (Figure 4) showed torque values after 50 consecutive contractions which were similar to those found in the control group. However, a significantly larger reduction in torque values after 50 contractions were found at the second examination compared to the first ($P < 0.002$), but not at the third compared to the second examination.
Macro EMG

Over the first 4 years there was a significant increase in relative Macro amplitude (Stålberg & Grimby 1995). Twenty out of 26 legs showed a further increase in relative Macro amplitude over the 8-year period (Figure 5), on average 16.7 (range 3-42). This increase did not reach statistical significance for the pooled material. The change in relative Macro amplitude (in percent) over a four-year period (from 0 to 4 years and 4 to 8 years) was plotted against relative Macro amplitude at the beginning of the period (Figure 6). There was an increase until a breakpoint of 20 times increase in relative amplitude. The legs with marked decrease in relative Macro amplitude over 8 years were unstable.

There was a positive correlation ($P < 0.05$) between present age and change in relative Macro amplitude over 8 years. There was no statistically significant correlation between the change in relative Macro amplitude over time and the age at acute poliomyelitis or time passed since acute poliomyelitis.
Furthermore, the FD parameter was increased in all muscles that had been investigated with Macro EMG. The increase in this parameter supports reinnervation in this study.

The jitter was assessed to test for the function of NM transmission. Impulse blocking was present in 60 percent of the investigated legs. When blocking was present it was seen in 18 percent of the motor end-plates. For each recording with blocking, approximately 30 percent of the consecutive discharges were blocked. Thus, in legs with blocking, the number of missing impulses was about 6%. There was no increase in jitter over the time period.

Figure 5. Relative Macro MUP amplitudes on the y-axis at the three examinations in the unstable and stable muscles respectively. Twenty out of 26 legs showed a further increase over the 8-year period. Note that the legs with marked decrease in relative Macro amplitude over 8 years belong to the unstable group. (From investigation II, © Wiley)
Figure 6. Change (in percentage) in relative Macro MUP amplitude over a 4 year period versus relative Macro MUP amplitude at the initial examination. The first and second 4 year period are in the same plot. The breakpoint for increase / decrease in relative Macro amplitude over time is around 20. lovess fitline (SPSS®) is indicated. (From investigation II, © Wiley)

Muscle biopsy

Muscle biopsy was performed in 10 legs (VL); of which 9 legs were classified as unstable.

The mean fiber area was increased in 7 legs, while the mean fiber area for all legs was $1.7 \pm 0.3$ times normal. There was no systemic pattern in the change of fiber area over time. There was no change in fiber type composition over the time period, the relative number of type I fibers were $40 \pm 12$ percent, $42 \pm 11$ percent and $45 \pm 13$ percent at the consecutive examinations.

Capillarization, expressed as the number of capillaries per fiber, decreased over time. However, there was no change over time for the number of capillaries per square millimeter, the number of capillaries in contact with each fiber or fiber area in relation to capillaries around each fiber.

There was no change in muscle enzymatic activity over the time period. However, CS showed low values over the time compared to controls (Figure 7). Only unstable legs were examined.
Figure 7. CS levels for 8 unstable legs at the initial and the last examination after 8 years. Dotted area indicates control values. All legs show decreased values. There is no change in CS level over the time period. (From investigation II, © Wiley)

Summary

Muscle strength decreased over time particularly for the unstable legs compared with the stable legs. The lack of central drive at maximal voluntary activation was 5.7 percent. Furthermore, endurance decreased over the first 4-year period. There was an increase in relative Macro amplitude over time seen mainly in the muscles with a relative amplitude lower than 20. At higher amplitudes there was a decrease over time. NM transmission failure was about 6 percent in legs with disturbed NM transmission, but there was no difference over time. The fiber area and type did not change over time, nor did the muscle enzyme CS. However, the number of capillaries per fiber decreased during the 8-year period.

To conclude

The continuous increase in Macro amplitude over time was due to reinnervation and not to muscle fiber hypertrophy. There is an upper limit for reinnervation that is associated with weakness.
Investigation III

In investigation III the finding of a normal EMG investigation in prior polio patients that showed new or progressive symptoms was investigated.

The patients were classified into five diagnosis groups:

1. Another diagnosis: Six patients were included in this group after reconsidering the diagnosis and rejecting the diagnosis of polio. Two patients suffered from cerebral palsy. The third patient had a diagnosis of central paresis of unknown cause. One patient suffered from a stroke and later spinal meningioma was a probable cause for the new symptoms. Another patient had had a GBS. The last patient in this group seemed to suffer from a hysterical reaction.

The neurophysiological findings (Table 5) consisted of central weakness in two patients, which was related to the new diagnosis. In the patient with earlier GBS the nerve conduction study indicated a polyneuropathy. In one of the patients which suffered from cerebral palsy a myopathic EMG was demonstrated, but this was taken as a coincidental finding.

2. Uncertain diagnosis of polio: Three patients were included in this diagnosis group. The history was very uncertain without any definite acute spell of symptomatology confirmed.

There were normal neurophysiological findings in this group.

3. Polio meningitis: Two patients were included in the group. Both had had signs of meningitis and suffered from weakness in the acute stage of polio.

The neurophysiological findings consisted of a low central drive during the EMG investigation for both patients. In one patient, slight neurogenic changes were taken as a sign of a later developed radiculopathy.

4. Suspected paralytic polio: Seven patients were included in this group. The dominating symptom in acute polio for the group was weakness. Neurophysiological findings consisted of elevated FD in one muscle with normal Macro amplitude. In another patient there were neurographic findings, which was compatible with a slight polyneuropathy. The neurophysiological findings were not related to clinical signs or symptoms.

5. Paralytic polio. Seventeen patients were included in this group. The dominating symptom in the acute spell was weakness for all patients. Neurophysiological findings showed decreased central drive in one case related to possible central involvement. In another patient the EMG and neurography was compatible with carpal tunnel syndrome (CTS) and a third patient showed neurographic findings fitting with CTS.
<table>
<thead>
<tr>
<th>New Symptoms</th>
<th>Other</th>
<th>Uncertain</th>
<th>Meningitis</th>
<th>Suspected polio</th>
<th>Paralytic polio</th>
</tr>
</thead>
<tbody>
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<td>Weakness</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Hemi-weakness</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td></td>
<td></td>
<td>5</td>
<td>9</td>
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<td>1</td>
<td></td>
<td>2</td>
<td>6</td>
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<tr>
<td>Sensory symptoms</td>
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<tr>
<td>Postural symptoms</td>
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<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td># Patients</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 5. EMG findings and new symptoms in the different diagnosis groups. Note the lack of different symptom profiles regarding new symptoms between the different diagnosis groups.

NCS = Nerve conduction studies, CTS = carpal tunnel syndrome.

Summary
A diagnosis other than polio was established in 6 patients. Polio meningitis was the cause of weakness in two cases. In three patients the diagnosis of polio was uncertain. Seven patients showed a suspicion of paralytic polio. In 17 patients there was a strong suspicion of previous paralytic polio without any EMG signs of degeneration of the AHCs.

To conclude
Normal EMG in patients with a history of polio could indicate that the original diagnosis may be incorrect. Furthermore, in some patients with a history of paralytic polio, the new symptoms are not associated with AHC death.
Investigation IV
In investigation IV Macro EMG and the patients’ assessment of symptoms was performed at two occasions 5 years apart. Also, a test-retest of Macro EMG reproducibility was performed.

Test-retest of Macro EMG

Controls
The difference in mean Macro amplitude between the investigations (during the test-retest) was –7.8 percent (P > 0.45). There was a correlation (r = 0.70, P < 0.01) between the test and retest amplitudes (Figure 8). The (mean) FD showed no difference between the test and retest.

Prior polio
The corresponding number in mean Macro amplitude difference for the prior polio patients was 6.9 percent (P > 0.33). They also showed a correlation (r = 0.91, P < 0.001) between the test and retest amplitudes. The test-retest showed no difference in FD.

Figure 8. Test-retest of Macro EMG, controls and prior polio. Each dot represents median Macro MUP amplitude from one tibialis anterior muscle. There is a significant correlation between the test and the retest amplitudes both for controls and prior polio patients. (From investigation IV, © Elsevier)
Macro EMG in study group

Study 1.
Twenty-six out of 28 TA muscles showed increased Macro MUPs compared to healthy controls. Twenty-six muscles showed elevated FD, while only one muscle showed a normal Macro EMG (normal MUP amplitude and FD).

Twenty-three out of 28 BB muscles showed increased Macro MUP amplitudes. Twenty-five BB showed increased FD, while only one BB muscle showed normal Macro EMG.

Change between study 1 and 2.
The relative Macro MUP amplitude in the TA muscle showed an increase of 18 percent (first study 7.2, second study 8.5, P < 0.05) over the time period (Figure 9), but FD did not change.

BB did not show any difference in either the relative Macro MUP amplitude nor the FD in the two studies. Macro EMG details are shown in Table 6.

There was no difference between the TA and BB at either study. The increase in Macro MUP amplitude described above could not be detected in this analysis, probably due to a large scatter of data.

There was no statistically significant correlation between a change in relative Macro amplitude over time and present age, age at acute poliomyelitis or time since acute poliomyelitis.

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Change in rel MUP ampl</th>
<th>Change in mean (%)</th>
<th>Intraindividual % change</th>
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</thead>
<tbody>
<tr>
<td>Rel MUP ampl</td>
<td>Rel MUP ampl</td>
<td>between study 1 and 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>7.2 (1.7-35)</td>
<td>8.5 (0.7-44.4)</td>
<td>1.3 (P&lt;.05)</td>
<td>18</td>
</tr>
<tr>
<td>BB</td>
<td>6.3 (1.6-23)</td>
<td>5.6 (1.3-20.7)</td>
<td>-0.7 (P&gt;.05)</td>
<td>-11</td>
</tr>
</tbody>
</table>

Table 6. Relative amplitude of Macro MUP amplitude in study 1 and 2, and the change between the two studies for TA and BB muscles. The values change for TA, but not for BB. (Modified from investigation IV, © Elsevier)
Figure 9. Change in relative Macro MUP amplitude in the TA and BB muscles versus age over time. Each line indicates one muscle. The left end of the line represent data at the first investigation, the right end represents the data at the last investigation. Ta shows increase over time, BB does not. (From investigation IV, © Elsevier)
Distribution of Macro MUP amplitudes

An effort was made to investigate if the relative amplitude increase was due to a loss of small amplitudes or if there was a general homologous increase in MUP amplitudes. However, a direct analysis on the intra-individual level regarding the change in the MU spectrum between the studies was hampered because the consecutive recordings represents two different MU populations. Nevertheless, we analyzed the distribution in muscles from 15 patients. A variable pattern was found in the TA muscle. Also the distribution of all individual MUP amplitudes from patients at consecutive investigations in the two muscles showed no systemic differences.

Clinical assessment

There was no difference in assessed weakness between the TA and BB muscles at the initial study. Five years later there was a difference in assessed weakness between the TA and BB (P < 0.05), weakness was dominant in leg muscles.

There was a difference in fatigue between TA and BB at both studies. Eleven patients reported new or increased pain; however, there was no correlation between the (new, added or present) pain and assessed (added, new or present) weakness.

Combination of results: Macro EMG versus weakness and fatigue

There was a correlation (P < 0.05) between relative Macro amplitude and both the initially assessed weakness and fatigue in both muscles. There was no correlation (P > 0.6) between the change in relative Macro amplitude on the individual muscle level (for both muscles) versus added assessed weakness and fatigue.

Summary

There was an increase in the relative Macro amplitude in the TA muscle over time, but not in the BB. This was associated with an increased subjective weakness in the TA over time, but the BB was less affected. There were no systemic differences in the distribution of MUP amplitudes in the follow-up study.

The test-retest of Macro EMG showed a high correlation of amplitudes between the test and retest. There was no difference in FD in the test-retest.
To conclude
There was a more pronounced denervation-reinnervation process over time in the TA than in the BB, which may be due to the different long term muscular activity between the two muscles.

Investigation V
In investigation V the reflex pattern in prior poliomyelitis was evaluated. Mono- and poly-synaptic reflexes were tested and their relation to force and AHC involvement was assessed.

Monosynaptic reflexes

**Tendon jerks**
Prior polio patients: Patellar tendon jerks were assessed in 25 subjects, exposing 49 quadriceps. Twenty-two patellar tendon jerks showed normal responses, 26 jerks were decreased and one was absent. Normal force was identified in ten of 24 quadriceps with decreased tendon jerks (force was not measured in two quadriceps).

Achilles tendon jerks were assessed in 25 subjects, exposing 50 triceps surae. Nineteen Achilles tendon jerks were assessed as normal, 29 were decreased and two were absent. Normal force was found in 12 of 27 triceps surae with decreased tendon jerks (force was not measured in two triceps surae).

Controls: All subjects (20) had normal patellar tendon jerks. Eighteen subjects had normal Achilles tendon jerks, while two subjects, ages 67 and 84 years, had slight reduced tendon jerks (the latter has been reported in a small number in elderly controls (Dick 2003)).

**T-response (Vastus lateralis muscle)**
Forty-four T-responses were recorded in the 25 polio patients. In the 20 controls, recording was made unilaterally.

There was no difference on group level between the prior polio patients and the controls in mean amplitude at rest, AA or JM. With AA and JM the amplitude increase compared to rest were the same for the prior polio patients and the controls. However, in the ANOVA test, the value of AA in the control group showed a significant change, while the value in the polio group did not.

There was no difference in latencies (at rest, AA and JM) between the prior polio patients and the controls. However, there was a significant shortening of the latencies at both AA and JM, which was the case for both prior polio patients and controls. There was a positive correlation between...
latency and age, however this correlation was not significant in the control group.

Separate analysis of the muscles that had a combination of normal force and reduced tendon jerks showed results of the T-responses that were compatible with results from the entire polio material.

**H-reflex**

H-reflexes were recorded in 25 prior polio patients (48 muscles). In the 20 controls the recording was performed unilaterally.

The H/M-ratio was lower in the prior polio patients than in controls, 14.5 percent and 29.7 percent respectively (P < 0.001). Furthermore, the mean M-max and the H-max were lower in the prior polio patients compared to controls. Twenty-two muscles in the prior polio group showed a present CMAP despite an H/M-ratio of 0.

The subgroup of polio patients with a combination of normal force and reduced tendon taps did not differ in H/M-ratio from that obtained for the whole polio material.

There was no difference in latency between the patients and the controls.

**Polysynaptic reflexes**

**Inter-limb descending muscle response**

Seventeen out of 25 prior polio patients showed ILRs. The shortest latencies were below 130 milliseconds, excluding one case. In 9 patients, stimulation of the upper limb gave a response in the contra-lateral VL, 8 of whom also exhibited ipsi-lateral responses.

ILR was not present in the controls.

**Startle, withdrawal and long loop reflex**

In addition to one control, eight prior polio patients had late responses that were classified as possible startle response (Landis & Hunt 1939; Yeomans et al. 2002). No stimulus was painful, therefore the responses were not classified as withdrawal reflexes (Hagbarth & Finer 1963).

It is unknown if the late responses, here classified as ILR, sometimes passed more central structures and should be called long-loop reflex (Kagamihara et al. 2003), however, independent of the mechanism, these responses were only seen in the prior polio patients and not in controls.

**CNEMG and Macro EMG**

Forty VL muscles were investigated with CNEMG in 22 prior polio patients. One muscle showed complete denervation, one muscle was classified as normal and thirty-eight muscles showed slight to pronounced neurogenic 56
findings. The relative CNEMG amplitude ranged from 1.1 to 16.4 times the normal value, with a mean of 4.8.

Forty-three GM muscles were investigated with CNEMG of which 39 were accepted for quantitative assessment in 23 prior polio patients. Four muscles showed normal EMG, while 39 showed different degrees of neurogenic findings. The relative amplitude ranged from 0.74 to 15.7 times the normal value with a mean value of 3.8.

Macro EMG was performed in 27 VL muscles (18 patients). All recordings had elevated mean relative Macro amplitudes ranging from 2.9 to 20.8 times the age matched controls with a mean of 7.3.

EMG was not performed in controls.

F-response
The F-response was analyzed in 8 prior polio patients (8 tibial nerves, abductor hallucis muscles). There was no difference in F-M minimal latency between the prior polio patients and age and height matched control data extracted from another control material (Puksa et al. 2003).

Force testing
Among the 48 quadriceps tested (in 24 prior polio patients), 29 muscles had normal force and 19 different degrees of reduced force. No muscle had a complete loss of function.

Among the 48 triceps surae tested (in 24 prior polio patients), 29 muscles had normal force, 18 had reduced force and one triceps surae had a complete loss of function.

The 20 controls had normal force in the quadriceps and triceps surae unilaterally.

Patients assessment of weakness
Sixteen (of 22 reporting) prior polio patients experienced weakness in 20 knee extensor muscle groups. Slight weakness was experienced in 4, moderate in 9 and pronounced weakness in 7 muscle groups.

No controls experienced weakness.

Combination of results
Force was significantly correlated with H/M-ratio (positive), T-response amplitude at rest (positive), briskness of patellar and Achilles tendon jerks (positive) and EMG score (negative).

There was no significant correlation between force and the presence of ILR.
Experienced weakness was significantly correlated with EMG score (negative) and force (positive).

Experienced weakness was not correlated with the presence of ILR.
EMG score was significantly correlated (negative) with H/M-ratio (Figure 10) and T-response amplitude at rest.

Figure 10. EMG in the GM related to H/M-ratio. There is a negative correlation (P < 0.02) between the H/M-ratio (x-axis) and the relative CNEMG (y-axis).

Tendon jerks were significantly correlated with T-response amplitude at rest (positive), H/M-ratio (positive) and H-M latency (negative). The presence of ILR was not correlated with tendon jerks in the quadriceps, EMG score in VL or the T-response.

Summary
The clinical reflexes, H-reflex and T-response were positively correlated with force and negatively correlated with degree of AHC loss. The H-reflex (H/M-ratio) was decreased compared to controls.
ILR was present in 68 percent of the prior polio patients. ILR was not correlated to force.
To conclude
There are two reflex disturbances in prior polio. The first is related to force and AHC loss, the other is not.
Discussion

Many of the results in this thesis are based on findings using an EMG method called Macro EMG. Therefore, this method has been evaluated regarding the correlation between the obtained parameters and MU characteristics (simulation studies in investigation I) and the methodological reproducibility (investigation IV).

In the simulation studies performed in investigation I and in a previous study, (Nandedkar & Stålberg 1983a) a correlation has been shown between Macro MUP amplitude and number and size of muscle fibers; therefore, it is well suited to studies of reinnervation. Additionally, a good correlation was found between the number of muscle fibers and CNEMG MUP in the simulation, but the correlation was lower than for Macro EMG. Thus, CNEMG is less suited for the estimation of MU size in prior polio patients.

The test-retest variability of 21 percent (intra-individual level) for Macro EMG amplitude in prior polio is slightly better than the reported 28 percent in a study regarding ALS patients (Bromberg et al. 1993). The corresponding number for motor unit number estimation (MUNE) and CMAP amplitude in that study was 32 percent and 21 percent respectively. Macro EMG was thus considered to be a better alternative to other methods available for MU studies, such as MUNE methods, twitch measurements or conventional EMG methods.

The reference material for Macro EMG was taken from an earlier study in healthy subjects of different ages (Stålberg & Fawcett 1982). No longitudinal study has been made in individual controls. The mean amplitudes of the Macro EMG show an age dependent increase, more so for the VL and TA muscles than for the BB muscle (Stålberg & Fawcett 1982). Therefore for each study the age matched MUP amplitude value has been given, known as the relative amplitude. Thus, the effect of age has been taken into consideration.

Macro EMG could be used for an estimate of the relative number of remaining motorneurons innervating the investigated muscle using the following formula (Stålberg & Grimby 1995):

\[
\text{Percentage of remaining motorneurons} = \frac{100 \times \text{relative mean fiber area}}{\text{relative Macro MUP amplitude}}
\]
While this formula is generally acceptable, a number of pitfalls must be observed. For example, if there is incomplete reinnervation, this formula gives an overestimation of the remaining motoneurons. Weakness is compensated with muscle hypertrophy in weakened polio muscles (Borg et al. 1988a; Grimby et al. 1989). In investigation II the relative mean fiber area increased 1.3-1.7 times (type I fibers) control values. The corresponding number was 2.1 in a different investigation (Borg & Henriksson 1991). In routine investigations of polio, no biopsy data is available and the relative mean fiber area is estimated to be 2, used in the formula. There is a risk for an under-estimation of the percent of remaining neurons if the actual muscle fiber hypertrophy is larger than this number, but usually the hypertrophy is less and the calculated number represents a maximal value. This relative number of remaining motoneurons is valuable information in the clinical evaluation.

When performing Macro EMG, usually only low threshold MUs are investigated due to the slight muscular activation during the investigation (Stålberg & Trontelj 1994). These MUs are smaller than later recruited MUs in healthy subjects, a fact that may influence the results with a severe loss of neurons or abnormal recruitment order. Furthermore, studies using voluntary contraction have a theoretical shortcoming, the degrees of reinnervation are only assessed in low threshold MUs. There are no conclusive reports published suggesting selective destruction of large or small motoneurons.
Weakness and new weakness

The patients with status post-polio also suffer from weakness in a stable phase. At the first examination of investigation II the stable legs showed weakness; 34 percent mean loss of strength compared to controls. Contrary to the stable patients, a considerable number of patients suffered from new weakness and developed PPS. The incidence for PPS in investigation II was 1/21 prior polio patients per year and in investigation IV the corresponding number was 1/23.

The Macro amplitude was increased as a sign of reinnervation, both in stable and unstable patients. The general EMG and biopsy findings indicated that the weakness in stable and unstable patients was mainly related to the loss of neurons with incomplete compensatory mechanisms, i.e. reinnervation and fiber hypertrophy. These mechanisms still can be very effective in some patients, with an estimated loss of up to 60 percent of neurons, that still did not result in to weakness (Dengler et al. 1989). When the loss of neurons is extensive, there is a loss of muscle strength (Einarsson et al. 1990). The most probable cause of this weakness is a loss of neurons with an incomplete reinnervation of orphaned muscle fibers.

The follow-up investigations had a general increase in MU size over time, which was more than expected from aging alone in the leg muscles. This was related to physical activity, but other reasons cannot be excluded.

There was also a limit of about 20 times increase in Macro EMG amplitude. At that point there seems to be a “breakpoint” for the mechanism of denervation / reinnervation which is related to weakness in prior polio. This indicates that the presence of extremely large average sized MUs predict new weakness.

With follow-up investigations where Macro EMG is performed there is the possibility to investigate the change in “spectrum” of MUP amplitude over time. However, it is not possible to follow the same MUs over time. With quantitative studies it is still possible to have reliable follow-up studies, comparing the results from many different MUs in a muscle. This information, together with findings from morphometry in muscle biopsies, could provide information about possible mechanisms for new weakness. For example, this information could answer the question if the new weakness is mainly due to loss of whole neurons or fragmentation of the MU or is it due to a mechanism other than the loss of muscle fibers?

The dominating picture of increasing Macro MUP amplitudes over time in MUs with increased FD indicated denervation / reinnervation, rather than a theoretical possibility of loss of small MUs. A fragmentation of MUs should give a reduction in the size of some MUs and increase in others. Our finding of general increase in MU size point in direction of a loss of motoneurons, rather than fragmentation as a general phenomenon. In later stages, with Macro MUP amplitude exceeding 20 times the normal, fragmentation may
be present. In addition to fiber grouping of both type I and II fibers, results from muscle biopsies showed single atrophic fibers, usually round. Groups of atrophic fibers were less common (Grimby et al. 1989). The biopsy results indicated a possible mechanism of fragmentation of the terminal axon sprouts, but also indicated group atrophy as a sign of loss of whole neurons. The biopsy findings over time showed no increase in frequency of atrophic fibers (Grimby et al. 1994). This result was explained by the slow process and other technical reasons (Grimby et al. 1994).

The possible cause of new weakness by fragmentation of MUs with excessive sprouting is discussed by Wiechers and Hubbel (Wiechers & Hubbell 1981) and Dalakas et al (Dalakas et al. 1986). The first group found SFEMG abnormalities that “may represent disintegration with aging in the reinnervated motor units” due to a greater metabolic demand of the reinnervated neurons. Dalakas et al found scattered angulated fibers without group atrophy in biopsies, in addition to absence of neurogenic jitter in the SFEMG findings interpreted as support for the fragmentation of MUs.

A consequence of the fragmentation of MUs without compensatory reinnervation would be a decrease of mean MU size over time, which is inconsistent with the general findings in investigation II and IV, but is consistent with the cases in investigation II that show extremely large MUs.

In summary, the Macro MUP amplitude does increase over time which is not an effect of increasing muscle fiber hypertrophy, instead, it is an effect of reinnervation. The main mechanism responsible for new weakness is thus most likely a further loss of whole neurons. However, in large MUs, fragmentation is a likely mechanism when the MU has reached a size when there is no possibility for the neuron to support all of its fibers.

There was a correlation between present age and change in relative Macro MUP amplitude over time in one of the longitudinal studies, but not in the other. There was a lack of correlation between the change in Macro over time and both age at acute poliomyelitis and time since acute poliomyelitis. This does not exclude a different time course for young and old individuals. The present material includes patients with poliomyelitis more than 20 years ago and of very different severity. No conclusions are drawn due to the diversity of results. In a small number of patients there was the possibility that the initial inflicted neurons later had a reduced safety margin resulting in later functional impairment without the presence of AHC degeneration measurable with EMG.

Some of the patients that did not show signs of AHC degeneration reported increasing symptoms of various types (weakness, fatigue, cold intolerance, pain) over time. However, this has not been assessed in this study.

Muscle fiber transformation and motorneuron firing properties could have effects on the strength, but probably to a lesser degree. This has not been a focus of this study.
The defects of the NM transmission studied as jitter and blocking at the EMG investigations only give rise to approximately 6 percent of the estimated weakness in patients with signs of NM transmission disturbance. This defect does not show a significant increase over time; thus, NM transmission defect does not seem to explain the increasing weakness over time.

There are two types of reflex disturbances in prior polio. First, the tendon jerk is reduced in some muscles, possibly related to reduced AHC excitability. The weakness is related to this disturbance, but the magnitude has not been quantified in this study. Furthermore, this has not been studied over time. The other reflex disturbance, the presence of ILR, is different from a withdrawal (Hagbarth & Finer 1963), startle (Chokroverty et al. 1992) or long loop reflex (Kagamihara et al. 2003) and is not related to weakness. ILR may either indicate a primary involvement of spinal interneurons or retrograde secondary changes of interneuronal connections as a response to the loss of AHCs.

The twitch interpolation performed in investigation II indicated a 6 percent loss of strength from lack of activation due to a central cause. This parameter was not studied over time.

Atrophy due to disuse is not the usual finding in status post polio. In contrast, the common biopsy finding was hypertrophy. However, weakness may be due to pain inhibition in the individual case, but cannot explain the general pattern of PPS because there was no correlation between weakness and pain in investigation II.

Fatigue

Mechanisms of fatigue may be different from those causing weakness. The cause of fatigue has not been investigated in great detail in this study, but some findings influence this parameter. In investigation II the endurance test revealed a decreased endurance at the first follow-up after 4 years. However, the isolated sessions (the initial and after 4 years) did not show any difference in endurance between patients and controls. When the “patient experienced” fatigue was assessed in investigation IV, there was an escalation of experienced fatigue over time.

The possible site of defect causing fatigue is discussed below.

On the muscular level a decrease in the concentration of the muscle enzyme CS was observed (in the biopsies in investigation II), but there was no decrease over time. Capillarization tended to be reduced over time. However, the results from this biopsy study did not allow any conclusions to be drawn regarding the relationship between biopsy findings and fatigue.

The NM transmission was assessed in another investigation (Stibrant-Sunnerhagen et al. 2000), not included in this study. That investigation dealt
with fatigue in post-polio. There was no difference in fatigue during a fatigue protocol between prior polio patients and controls. However, the recovery of force after the fatigue protocol was slower for the prior polio patients, which has also been reported by others (Rodriquez & Agre 1991). This could be due to central and/or peripheral fatigue. That investigation did not show any signs of disturbance of the NM transmission as a cause for fatigue.

Thus far there is no consensus on the reason for fatigue in prior polio and from our studies we were unable to make conclusive statements. Unable to pinpoint a single reason may indicate that fatigue in prior polio has a multifactorial cause and may differ between patients.
Conclusion

Weakness and new weakness
The weakness in prior polio is mainly due to a loss of motorneurons with incomplete compensatory mechanisms of reinnervation.

Failure of the central drive and NM transmission only contribute a minor degree.

In a small number of patients a possible functional impairment without AHC death seems to cause later weakness.

The main mechanism for new weakness seems to be an ongoing loss of whole neurons as a sign of exaggerated physiological age dependent loss of motorneurons. Also fragmentation of MUs is likely when these have reached a size where there is no possibility for the neuron to support all of its’ fibers.

The loss of motorneurons over time is partly activity dependent.

Fatigue
Patients with status post-polio often show fatigue. The reasons are multifactorial, but the relative importance of peripheral and central causes could not be established, which is partly due to inter-individual differences.

EMG methods of choice to assess changes in polio muscles
Assessment of MU size should be performed with Macro EMG in combination with an assessment of the micro-physiology of the MU preferably.

Macro EMG is also recommended in follow-up investigations when evaluations of MU parameters are of interest.

In the assessment of concomitant disorders, the CNEMG is of value in addition to Macro EMG.

Importance of the studies on the management of patients with prior polio
Muscular overuse may be an important factor that accelerates motorneuron loss over time in prior polio. The risk for overuse should be considered in the activities of daily living or during physical training. Extremely large MUs predict new weakness. Macro EMG could be used for prognosis. This is also of importance in muscles not clinically weakened.
Future directions

Planning for tomorrow has several directions:

- In prior polio, further investigations regarding the relationship between MU properties and the compensatory mechanisms including the evaluation of the effects of activity, training and medication.
- Underlying factors for neural degeneration and accelerated aging should be studied, including immunological and biochemical techniques.
- MU number estimation techniques should be applied in long-term studies to study the peripheral loss of MUs and methods for the assessment of central activation to study central fatigue and central changes as secondary phenomena to the loss of muscular activity (plasticity).
- In other neurogenic lesions (spinal muscle atrophies, syringomyelia, plexus lesions, mono neuropathies) there may sometimes be a clinical situation of increasing symptoms despite no obvious additional lesions. Is there a parallel to the PPS? Investigations regarding the pathophysiology for the additional symptoms in such lesions are planned.
Summary in Swedish – sammanfattning på Svenska


Huvudsyftet med denna studie var att klargöra vilken mekanism som ligger bakom den stationära samt den sent uppträdande progredierande muskelsvagheten efter genomgången polio.

Studie 1
Poliomyelit angrep bl. a. främre delen av ryggmärgen där de motoriska framhornscellerna är belägna. Funktionen av dessa kan studeras med elektromyografi (EMG).

Syftet med studie 1 var att utvärdera vilken EMG metod (koncentriskt nål EMG (CNEMG) eller Macro EMG) som är bäst för att studera den motoriska enhetens storlek som tecken på grad av reinnervation. Denna retrospektiva studie inkluderade 121 poliopatienter.

EMG undersökning med båda metoderna utvärderades och även simulation av de båda metoderna utfördes för kvantitativa analyser.

Studien visade att Macro EMG metoden både visade förändringar i den motoriska enhetens storlek oftare än CNEMG samt att Macro EMG metoden korrelerade bättre till muskelfiber parametrarna som avspeglar den motoriska enhetens storlek.

Sammanfattningsvis visade studien att Macro EMG är bättre än CNEMG för bestämmande av den motoriska enhetens storlek.
Studie 2
Syftet var att studera orsaken till svagheten efter genomgången polio samt att undersöka de kompensatoriska processernas effektivitet. Vidare skulle sambandet mellan symtom, muskulär svaghet och de kompensatoriska processerna (muskelhypertrofi och kollateral reinnervation) undersökas.

Patienter följes under 8 år vid 3 tillfällen. Studien inkluderade undersökning av den neuromuskulära transmissionen, reinnervation, muskeliopsier samt muskelkraftsmätning.

Studien visade reducerad muskelkraft under tidsperioden, speciellt för de patienter som rapporterat sänkt kraft i undersökta muskler. Man kunde också visa en reduktion av muskulär uthållighet under den första 4-års perioden. Macro EMG undersökningen visade ökning av amplituden i de muskler där medelamplituden vid första tillfället ej översteg 20 gånger det normala. De muskler som visade en Macro amplitud överskrivande 20 gånger det normala minskade i macro amplitud till nästa undersökningstillfälle, vilket också var relaterat till kraftförlust. Centrala orsaker till kraftförlust var 6 %.

Störning i neuromuskulär transmission bidrog till mindre än 6 % kraftförlust, och ingen ökning iakttogs över tid. Muskelbiopsierna visade vanligen hypertrofi, dock utan förändring över tid. Antal kapillärer per muskelfiber minskade över tid. Muskelenzymet citrat syntetas var sänkt men ändrades inte över tidsperioden.

Sammanfattningsvis förelåg en kraftförlust över tid som berodde på pågående motorneuron förlust utöver den normala åldersbetingade förlusten. Vidare berodde den initiala ökningen i macro amplitud på reinnervation och i mindre omfattning på muskelfiberhypertrofi. Det förelåg en övre gräns för reinnervation som var associerad med ny svaghet.

Studie 3
Efter genomgången paralytisk polio återfinns i stort sett alltid tecken till genomgången reinnervation vid EMG undersökningen. I 5 % gjordes det ovanliga fyndet av en normal EMG undersökning i kombination med anamnes av paralytisk polio och nya symtom. Studien syftade till en närmare undersökning av dessa.

Sammanlagt 688 patienter undersöktes med EMG, 35 patienter med normalt EMG (eller minimalt avvikande EMG beroende på annan orsak än polio) inkluderades för fortsatt undersökning i form av genomgång av patientjournal, samtal med patienter och med tidigare och nuvarande behandlade läkare.

Av dessa 35 patienter visade sig 6 patienter ha en annan diagnos. I 2 fall bedömdes poliomeningit vara orsak till symtomen. I 3 fall var diagnosen polio mycket osäker. Sju patienter misstänktes ha resttillstånd efter paralytisk polio. I 17 fall förelåg en stark misstanke på resttillstånd efter paralytisk polio.
Sammanfattningsvis visade studien att en annan diagnos kan föreligga vid normalt EMG hos ett mindre antal patienter med anamnes på genomgången polio. Hos en del patienter med genomgången paralytisk polio föreligger symtom som inte är associerade med framhornscells degeneration.

Studie 4
Syftet med studien var att undersöka i vilken grad muskulär aktivitet påverkar utveckling av ny muskelsvaghet.

Macro EMG utfördes i tibialis anterior som representerade en fysisk aktiv viktbärande muskel och biceps brachii som representerade en ej viktbärande muskel. Macro EMG resultatet relaterades till patienternas skattade symtom vid 2 undersökningsställen med en medeluppföljningstid av 5 år. Vidare utfördes en kontroll av reproducerbarhet av Macro EMG, både i polio patienter samt kontroller.

Studien visade en ökande Macro amplitud i tibialis anterior över tid associerat till en kraftförlust på gruppnivå. Det förelåg ingen skillnad i Macro EMG amplitud över tid i biceps brachii. För att utvärdera dessa resultat utfördes test-retest av Macro EMG. Upprepad undersökning med Macro EMG visade hög reproducerbarhet, både med avseende på Macro amplitud samt fiberdensitet.

Sammanfattningsvis föreligger tecken på en mer uttalad pågående denervations-reinnervations process över tid i den mer aktiva tibialis anterior än i den mindre belastade biceps brachii muskeln.

Studie 5
Syftet med studien var att utvärdera reflexmönstret hos patienter med genomgången polio samt att relatera detta till muskelkraft samt motorneuron förlust.

Mono- samt polysynaptiska reflexer inklusive sk interlimb reflex (ILR) samt manuell muskelkraft undersökes hos både poliopatienter och hos ålders- och längdmatchade kontroller.

Studien visade att de monosynaptiska kliniska senreflexerna, H-reflexen samt T-responset var positivt korrelerade till muskelkraft samt negativt korrelerade till motorneuronförlust. ILR förelåg i 68 % av patienterna med genomgången polio men ingen av kontrollerna uppvisade förekomst av denna reflex. ILR var inte korrelerad med muskelkraft.

Sammanfattningsvis förelåg tecken till två olika reflexstörningar vid genomgången polio. De monosynaptiska reflexerna är relaterade till muskelkraft och motorneuronförlust, men inte ILR.
Konklusion
Svagheten efter genomgången polio beror huvudsakligen på förlust av motoneuron samt på att den övre gränsen för de båda kompensationsmekanismerna reinnervation och muskelfiber hypertrofi är överskriden. En mindre del av svagheten kan tillskrivas centrala mekanismer eller defekt funktion i den neuromuskulära transmissionen. Hos ett mindre antal patienter är inte svagheten relaterad till degeneration av framhornseller.


Det fanns tecken till sänkning av den muskulära uthålligheten över tid. Ingen specifik mekanism för detta kunde säkerställas.

Överbelastning av musklerna kan vara en viktig orsak till accelererad förlust av motoneuron. Övervägande av denna risk bör göras vid instruktioner angående allmänna dagliga funktioner samt träning.

Extremt förstorade motoriska enheter kan indikera risk för utveckling av ny svaghet, en viktig komponent i post polio syndromet; här kan Macro EMG undersökningen användas i prognostiserande syfte.
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