Pathophysiology of muscular changes in post-polio syndrome and consequences for physical mobility

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Section A

Introduction

Chapter 1

General introduction

Acute paralytic poliomyelitis is a highly infectious disease that occurs in 0.1 to 2% of people who are infected by the poliovirus.^{1,2} Clinically, it involves a progressive loss of muscle strength that develops within hours and usually progresses for 2–3 days. Legs are more commonly affected than arms and the extent of muscular involvement may vary from one paretic muscle or muscle group to quadriplegia and respiratory failure.^{2,3} If the victim survives, the acute illness is followed by a recovery phase of up to 3 years, although most of the strength recovery occurs in the first 8 months.³ The neurological deficits that persist after the recovery phase generally remain stable for many decades.

The death rate from acute polio was considerable in the first half of the last century as mass epidemics took thousands of victims and respiratory failure could not be prevented until the development of mechanical ventilators (e.g. in 1952 58,000 people were paralysed and 3,000 died in the US alone).²⁴ The disease mainly affected young children (<3 yrs) who had not yet acquired immunity against the virus.⁵ As a result, for the survivors, the acute and recovery phase of the illness often occurred during an important period of (musculoskeletal) growth, resulting in many secondary, often asymmetrical growth and development disorders of the musculoskeletal system in addition to the residual paresis. Mass vaccination programmes following introduction of the Salk vaccine in 1955 and the oral Sabin vaccine in 1961 signalled the end of major epidemics in the western world, eventually leading to a polio-free USA in 1979 and European region in 2002. In some other parts of the world endemic polio is still prevalent, although the WHO global initiative to eradicate the disease permanently is making good headway.⁶ Perhaps because of this, the fear of polio has eased in developed countries in recent years. In the 1950s however polio, also known as "the crippler", had the power to terrify. It was common for swimming pools, churches and cinemas to close during polio season and governments on occasion resorted to extreme and misguided measures, such as spraying entire cities with DDT.⁴ The present-day disremembering of the severity of the disease is most evident in the alarming number of anti-vaccination groups that have sprouted in the last decade, following publication of a refuted and since retracted study describing a potential link between measles-mumps-rubella vaccines and autism.⁷

Post-poliomyelitis

In the late 19th century it became clear that some polio survivors experienced new symptoms after many years of stable functioning.⁸ It wasn't until the 1980s however, that a wave of research into the epidemiology and possible causes of these new problems was initiated,

driven by reports of new deterioration in the multitude of survivors of the last mass epidemics.⁹ These new complaints included new muscle weakness, post-exercise fatigue, loss of muscle mass, muscle and joint pain, cramps, cold intolerance, generalized fatigue, and less frequently respiratory problems.^{10,11} The confusing number of terms that were used to describe the varying combinations of new symptoms people experienced lead to the classification of post-polio syndrome (PPS) by Halstead and Rossi in 1985.¹² Currently, PPS is defined as a neuromuscular disease (NMD) that occurs 25–40 years after acute polio and is characterised by progressive loss of muscle strength and/or abnormal muscle fatigability. There are no pathognomonic findings that confirm the diagnosis, instead it is defined by the presence of the combination of clinical features described in Box 1.1.

Box 1.1 Criteria for post-polio syndrome (PPS), March of Dimes, 2001¹⁰

- Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).
- A period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurological functioning.
- Gradual or sudden onset of progressive and persistent new muscle weakness or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain. Sudden onset may at times follow trauma, surgery, or a period of inactivity. Less commonly, symptoms attributed to PPS include new problems with breathing or swallowing.
- Symptoms that persist for at least a year.
- Exclusion of other neurological, medical, and orthopaedic problems as causes of symptoms.

There are currently an estimated 15,000 people in the Netherlands and 10–20 million worldwide living with the consequences of polio many of them can be expected to develop PPS. Estimates for the occurrence of PPS vary widely, from 15 to 80%, depending on the criteria applied and populations studied.¹¹ So despite the fact that polio is for the most part a 'forgotten disease' in the western world, there are still large numbers of people world-wide who can be expected to experience further neuromuscular decline for decades to come. The decreased physical mobility and restricted social participation this entails comes at huge personal and societal cost. In various studies among polio survivors in developed countries, most are or were employed, but reduce working hours earlier and retire sooner

than peers leading to loss of income and more dependence on disability benefits.¹³ Methods of prevention or treatment of PPS would therefore be very welcome. Therapies thus far have however yielded few positive results and the search for different approaches continues.¹⁴ For the development of effective intervention programmes, understanding the aetiology of the disease, its nature and rate of progression is essential.

Pathophysiology

Despite the many studies describing the occurrence of new symptoms in PPS patients, the pathophysiology of muscle weakness in PPS still remains an issue of debate.⁵ In acute poliomyelitis, viral invasion of the central nervous system (CNS) results in the destruction of motor neurons in the anterior horns of the bulbar and spinal cord regions. Consequently, the entire motor unit (MU) (Figure 1.1A), which consist of the motor neuron and its corresponding axons, endplates and skeletal muscle fibres, becomes dysfunctional. The denervated muscle fibres are now 'orphaned' resulting in muscle paresis or paralysis (Figure 1.1B). In the recovery phase damaged motor neurons can regain some of their function or alternatively neighbouring unaffected motor neurons can adopt the orphaned muscle fibres leading to full or partial recovery of muscle strength (Figure 1.1C).^{1,15,16} Meanwhile, the muscle fibres which are not reinnervated atrophy or are subject to fatty invasion, leading





Schematic representation of the motor unit in healthy state (A), after acute poliomyelitis has destroyed a motor neuron (B) and after a neighbouring motor neuron has adopted the 'orphaned' muscle fibres during the recovery phase. Adapted from Gawne and Halstead, 1995.¹⁵



Figure 1.2 CT-images showing disruption of muscle architecture in PPS.

CT-images of a 53 year old polio survivor with new complaints of muscle weakness after 50 years without noticeable paresis. There is extensive atrophy and fatty invasion of the femoral biceps, gastrocnemius and soleus muscle of the right leg. Adapted from Maeda et al., 2006.²⁰

to a disruption of the muscle architecture¹⁷⁻²⁰ (Figure 1.2). Consequently, muscles of polio survivors function with a reduced number of MUs,²¹⁻²³ which can be enlarged up to more than 20 times those of healthy subjects,^{18,21,24} and show structural abnormalities.¹⁷⁻²⁰

In the most accepted hypothesis proposed in 1981 by Wiechers and Hubbell, the late decline of muscle strength in PPS is suggested to result from excessive distal axonal degeneration of these enlarged MUs after many years of a precarious balance between re- and denervation.¹⁶ Evidence for this theory has come from muscle biopsy and single fibre EMG studies. Biopsy studies demonstrated isolated atrophy of muscle fibres (MU size diminution) rather than the loss of whole MUs,^{16,25,26} while EMG studies revealed neuromuscular transmission defects indicative of ongoing de- and reinnervation.^{16,25,27} Longitudinal studies to date have however not yet been able to confirm this hypothesis, as average MU size increased or remained stable over time, except in a very few patients with exceptionally large initial units.^{18,28-30} Furthermore, loss of whole MUs has been reported, although it is as yet unclear if this happens at a faster rate than in healthy controls.^{23,31,32} These studies however had some shortcomings which could explain the unexpected results, such as a small number of participants with PPS and a short follow-up duration,^{28,29} inclusion of non-symptomatic patients and those who had contracted polio later in life (and therefore with potentially more residual capacity

for reinnervation at the time of measurement),^{18,23,29-31} and the lack of a control group.^{18,28-31} The conflicting evidence so far warrants further research into the role of axonal loss in the pathophysiology of strength decline in PPS.

If it is confirmed that net distal axonal degeneration/denervation takes place in PPS patients at a higher rate than in healthy controls, then the question remains why this happens. Wiechers and Hubbell originally proposed the 'overuse' or 'metabolic theory', which assumes there is a limit to how long a motor neuron can sustain the increased metabolic demands required by its increased size.¹⁶ More recently, the 'inflammatory theory' has gained more attention. This theory proposes that an ongoing inflammatory process in the CNS, resulting from persistence of viral RNA particles, might trigger the attrition of nerve endings.³³ Studies to date have found evidence of immunological and inflammatory activation in the spinal cord,^{34,35} muscle,³⁶ and vascular system^{37,38} decades after the acute infection, and the presence of oligoclonal IgG and IgM bands in CSF^{39,40} and inflammatory markers, or cytokines, in peripheral blood and CSF of PPS-patients.^{41,45} Expression of cytokines TNF-alfa and IFNgamma mRNA in central nervous system cells has moreover been shown to decline after IVIG treatment.⁴³ The connection between these findings and the clinical manifestations of PPS have however remained tenuous and no study so far has explored the relationship between the presence of inflammatory markers and denervation.^{14,33}

Physical mobility problems

Loss of strength is clinically relevant because it can influence the ability to perform activities of daily life and the extent to which a person is able to participate in society.⁴⁶⁻⁴⁸ Even though average strength appears to decline relatively slowly in PPS, with studies reporting losses of 1–2.5% per year,^{31,49,50} the cumulative loss over several decades is substantial and the functional consequences of this loss may be great as patients lack strength reserves.⁵¹ As the lower limbs are typically disproportionally affected by polio, further loss of muscle strength often primarily translates into physical mobility issues, such as difficulty walking, stair climbing, rising from a chair and using transportation devices.⁵² Physical mobility might be still further impeded by the generalised fatigue, muscle and joint pain and cold intolerance which are also frequently reported by polio survivors with and without PPS.^{46-48,52,53} In addition, all these symptoms are known risk factors for falls in elderly people and patients with neuromuscular diseases.⁵⁴⁻⁶⁰ Thus, polio survivors might be at risk of frequent falls and a fear of falls, both of which can further reduce physical mobility and participation in

activities of daily life.^{46-48,53,56,61} Because of all these potential disadvantages of loss of physical mobility, it is important to properly understand prevalence and rate of progression of these problems among polio survivors. Currently however, the rate with which physical mobility deteriorates, the magnitude and severity of the problem of falling and aetiology of falls, and to what extent the loss of muscle strength contributes to these problems, are still issues of debate.^{5,62}

Firstly, prospective studies to date have reported conflicting rates of decline of physical mobility in polio survivors (0-2% per year).^{49-51,63-67} Also, the direction of the change in physical mobility did not always match expectations based on concomitant strength changes.^{50,51,63-65,67} However, high quality long-term studies are scarce and the existing studies included patients with a wide array of initial deficits and used a great variety of different outcome measures to measure physical mobility. There is a need for more long term studies among symptomatic patients. Secondly, studies of fall frequency among polio survivors to date have confirmed the hypothesis that falling is a problem in this group, with 50-84% of participants reporting at least one fall each year.^{56,62,68-70} Figures pertaining to consequences of falls in polio survivors are equally alarming. Studies have reported 61% injuries requiring medical attention, 35-38% fractures and 77–95% fear of falling, with prevalence varying according to the type of population included and length of the study period.⁶⁸⁻⁷⁰ Much less is known about risk factors for falls in polio survivors, since only muscle weakness and fear of falling have been expressly studied in relation to falls in polio survivors.56,68 In other populations many additional risk factors for falls have been confirmed and successfully targeted in fall intervention programmes. The potential success of such a programme among polio survivors depends on whether or not circumstances of falls and associated factors are comparable.

Aims of the thesis

Designing successful intervention strategies depends on accurate knowledge of the pathophysiology and the nature of the disease, and of the connection between these and the rate of progression of symptoms. The aims of this thesis are to:

• Gain more insight into pathophysiological mechanisms underlying loss of muscle strength in PPS by investigating changes in muscle architecture, long-term changes in MU-size, presence of inflammatory markers, and the relationship between these findings and long-term changes in muscle strength.

- Assess the long-term rate of decline in physical mobility in relation to strength decline and to investigate potential predictors of the rate of deterioration of physical mobility in PPS.
- Establish the magnitude and severity of the problem of falling, the circumstances of falls and associated factors in polio survivors in the context of their neuromuscular decline and physical mobility problems.

Outline of the thesis

Section B focusses on the pathophysiology of muscular changes in PPS. **Chapter 2** describes the changes over 10 years in MU-size and muscle strength in quadriceps muscles of PPS-patients with quadriceps dysfunction, compared to healthy controls. The relationship between the declines in these two measures is explored in order to investigate the hypothesis that strength decline in PPS results from excessive distal axonal degeneration of enlarged units.

Theoretically, denervation (**chapter 2**) leads to a disruption in muscle architecture through gradual steatosis and fibrosis of muscle tissue, which in turn leads to muscle weakness. In **chapter 3**, alterations in muscle architecture are quantified using muscle ultrasound and compared to findings in muscles of healthy controls. The potential usefulness of muscle ultrasound for assessing disease severity and progression in PPS is investigated by relating the ultrasound findings to muscle strength values.

Chapter 4 explores the hypothesis that the denervation and muscular changes in PPS are the result of an ongoing inflammatory process. To this end, the levels of circulating inflammatory mediators in the bloodstream in PPS-patients are compared to those of healthy controls, and the relationships between these inflammatory mediator levels and declines in MU-size, muscle strength and physical mobility over time are investigated.

In **section C** we focus on physical mobility problems in polio survivors. First, the study in **chapter 5** describes how walking capacity and self-experienced physical mobility change over 10 years in PPS-patients with quadriceps dysfunction and explores whether large declines can be predicted ahead of time. Then, **chapter 6** focuses on investigating the frequency, circumstances and consequences of falls in polio survivors, as well as which factors are associated with falling. This knowledge is essential for the design of effective intervention programmes.

The general discussion in **chapter 7** in **section D** reflects on the main conclusions and methodological aspects of this thesis. In addition, the clinical implications of this research and future research prospects are considered.

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Section B

Pathophysiology of muscular changes in post-polio syndrome

Chapter 2

Loss of motor unit size and quadriceps strength over 10 years in post-polio syndrome

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Abstract

Objective: To investigate whether strength decline in post-polio syndrome (PPS) results from excessive distal axonal degeneration of enlarged motor units.

Methods: We assessed changes over 10 years in isometric quadriceps strength, mean motor unit action potential (MUAP) size, root mean squared (RMS) amplitude, and level of interference (LOI) in 47 patients with PPS and 12 healthy controls, using high density surface EMG. At baseline, all patients had symptomatic quadriceps dysfunction, evidenced by transmission defects on single-fibre EMG.

Results: MU size and strength declined significantly by 20% and 15%, respectively in patients with PPS. Those with the largest initial MU sizes exhibited the greatest losses of mean MU size (27%) and proportional decreases in quadriceps strength (23%). Initial strength, change in LOI and change in RMS amplitude together explained 35% of the variability in strength changes in patients. MU size of controls did not change, although they lost 29% strength.

Conclusion: MU size and strength declined concomitantly in a homogeneous cohort of patients with PPS and quadriceps dysfunction. This long term follow-up study provides evidence that size diminution of enlarged MUs combined with a reduced number of active MUs contributes to the gradual strength decline in PPS.

Introduction

Post-poliomyelitis syndrome (PPS) is a neurological condition that occurs 25–40 years after acute polio and affects a large proportion of the estimated 20 million polio survivors worldwide.¹ In PPS, muscle strength declines at a rate of 1 to 2.5% annually.²⁻⁴ Based on studies that demonstrated isolated atrophy of muscle fibres rather than the loss of whole motor units (MUs), the loss of strength is thought to result from excessive distal axonal degeneration of pathologically enlarged MUs (MU size diminution).⁵⁻⁷ Despite wide acceptance of this theory, recent electromyography (EMG) studies have reported the opposite: group increases or no change in average MU size over time along with loss of whole MUs.^{2,8-11} The absence of evidence for loss of MU size in PPS so far, besides sporadic findings of MU size and strength diminution in people with very large initial units,^{8,9} warrants further research into the role of axonal loss in the pathophysiology of strength decline in PPS.¹²

In 2000, based on high-density surface EMG (HD-sEMG) measurements, we observed low strength and greatly enlarged MUs in the vastus lateralis muscles of 66 patients with PPS that had proven quadriceps dysfunction, compared to 13 healthy controls.^{13,14} The present study investigated this homogenous cohort 10 years later and compared changes in MU size and muscle strength with those in healthy controls. We hypothesised that both MU size and muscle strength would decrease over time; that the rate of decline of these two variables would be related in patients with PPS, with the greatest declines occurring in those with severely enlarged MUs at baseline; and occur at a higher rate than in healthy controls.

Methods

Participants

Sixty-six adults with PPS that had completed HD-sEMG measurements in a randomised controlled trial of pyridostygmine between 1999 and 2001, were invited to participate in the present study in 2010.¹⁴ Thirteen healthy controls that had undergone HD-sEMG measurements during the same period were also approached for retesting.¹³ The criteria for the diagnosis PPS were an onset of progressive and persistent new weakness and/or abnormal muscle fatigability in polio survivors, after a period of stable neurological functioning, and the absence of other medical conditions that could explain the symptoms.¹ In this study, all individuals with PPS specifically had symptoms of PPS in either one or both quadriceps muscles at baseline. The patients also showed evidence of neuromuscular transmission

defects on a single-fibre EMG, indicative of ongoing denervation and reinnervation, and they had no important comorbidities. Detailed inclusion and exclusion criteria are described elsewhere.¹⁴ No new inclusion criteria were applied in the present follow-up. The only new exclusion criterion was the presence of any newly developed disease that affected voluntary control of the quadriceps muscle under investigation. All participants provided written informed consent, and the study was approved by the institutions' Medical Ethics Committee.

Study design

In this prospective cohort study, all participants underwent strength and HDsEMG measurements at baseline (2000) and follow-up (2010). Baseline data was obtained during the pyridostigmine trial before starting medication.¹⁴ Measurements were performed on the strongest symptomatic quadriceps muscle of each participant at baseline, and the same leg was tested at follow-up. In healthy controls, the strongest leg was chosen unless unilateral joint or muscle problems were present.

Measurements

The measurement protocol was as described previously.¹³ Briefly, a rectangular electrode grid composed of 130 gold-coated electrodes (electrode diameter: 1.5 mm; interelectrode distance: 5 mm), was placed over the vastus lateralis muscle, such that 10 columns with 13 electrodes each were positioned parallel to the muscle fibres. A reference electrode was placed on the patella. Monopolar signals were recorded, amplified, bandpass-filtered, and analogue-to-digital-converted with a multichannel amplifier system; the BioSemi Mark-6 was used in 2000 (bandwidth 3–400 Hz, sampling rate of 2000 Hz); in 2010, a similar system was used: the passive version of the BioSemi ActiveTwo (bandwidth DC-400 Hz, sampling rate of 2048 Hz).

Peak knee extension force was defined as the highest of three isometric maximal voluntary contractions (MVCs). MVCs were performed on a hard-surfaced, fixed chair dynamometer with the knee and hip flexed at 90 degrees. The lower leg was strapped to a lever arm containing force transducers and visual feedback was provided by displaying the attained force on a screen.

Force and HDsEMG recordings were synchronised using a common time code. HDsEMG data was high-pass filtered (10 Hz, fourth-order Butterworth filter) and stored for offline

analysis. Single motor unit action potentials (MUAPs) were extracted from bipolar EMG recordings of five, 30-s contractions between 5–20% MVC with a new, semi-automated software programme¹⁵ based on the principles used in manual analyses.¹⁶⁻¹⁸ Results obtained with automated detection were highly correlated to results from manual decomposition of similar real data.¹⁵ To exclude variability in analysis techniques, all baseline data were re-analysed according to a standard protocol by the first author with this programme. After removing duplicate MUAPs, the area under the curve of each remaining MUAP was determined over a period of 50-ms of the monopolar signal, from the electrode nearest the endplate zone (Figure 2.1). MUAP sizes were calculated after MUAP extraction had been completed for all participants at both time points; this eliminated the possibility of investigator bias. The average area under the curve of all detected single MUAPs (the mean MUAP size) was calculated for each patient. The accuracy of MU size determination based on MUAPs extracted from HD-sEMGs has been verified extensively.^{16,18,19}

In addition, the raw HDsEMG signal at 60% MVC was analysed to identify complementary MU characteristics related to strength production and maintenance. All variables were



Figure 2.1 Example of a MUAP size calculation from the monopolar signal.

This is an example of a monopolar MUAP over the electrode grid. The asterisk indicates the electrode with the highest negative peak amplitude, i.e. nearest the endplate zone. The area under the curve over the 50 ms period represented the MUAP size.

determined from signals in the electrode column with the highest mean signal amplitude, over a 2-s segment of the HDsEMG-signal, taken during the first 10-s of a stable 60% MVC.

MU size calculations at 5–20% MVC are biased towards type I MUs; consequently, we investigated root mean squared (RMS) amplitudes under high force conditions for an additional indication of the average MU size, measured when all MU types were active. Also, the level of interference (LOI) provided information about the number of active MUs. The LOI was defined as the percentage of the total recording time that consisted of segments of electrophysiological activity, i.e. bipolar turns that exceeded the noise threshold.¹³ Data from 60% MVC was chosen over 100% MVC, because many patients with PPS were unable to sustain a stable maximal contraction.

Statistical analysis

Statistical analysis was performed with the SPSS statistical software package (version 19.0.0.1). The primary outcome measures were the changes over 10 years in mean MUAP size (mV*ms) and knee extension MVC (Nm). Secondary outcome measures were the changes in RMS amplitude (mV) and LOI (%). The outcome measures were investigated in patient and control groups, and in the subgroup of patients with initial MUAP sizes in the upper tercile. The populations were expressed in percentages, means with standard deviations, or medians with interquartile ranges (IQRs). All change parameters were normally distributed; thus, paired samples t-tests were used to test for significance of change over time, and independent t-tests to test for significance of group differences. Pearson's correlation coefficient was used to test the association between age and the degree of change in primary outcome variables. An explanatory model for the change in maximal strength was constructed with a forward stepwise linear regression analysis to assess the roles of MU size and the number of active MUs. The independent variables were maximal strength at baseline, change in RMS amplitude at 60% MVC, and change in LOI at 60% MVC. Significance was set at p<0.05.

Results

Participants

Forty-seven patients (71%) with PPS and 12 healthy controls (92%) were included in the analysis. Non-participants were untraceable (n=6), deceased (n=2), unwilling or unable

(n=7 + 1 control), or excluded for co-morbidities that may have affected the quadriceps under investigation (n=3). One patient with PPS was non-compliant with the measurement protocol and was excluded from all analyses. Three controls and two patients with PPS were excluded from parts of the analyses due to technical errors (Table 2.1). The mean ages were similar in PPS (52±8) and control groups (48±14, p=0.577); both groups had slightly more women than men (66% and 67%, respectively). At the time of the polio infection, the median age was 2 (IQR: 1–4) years; the average time since polio was 49±9 years.

Motor unit characteristics

At baseline, the MUAPs were significantly larger in the PPS than the control group (p<0.001). Over 10 years, the mean MUAP size decreased by 20±44% in the PPS group, but remained stable in controls (Table 2.1 and Figure 2.2). Both the greatest MUAP reductions and increases occurred in the patients with the largest initial MUs, i.e. those with the most severely affected muscles at baseline (Figure 2.3 and Table 2.1). No significant correlations were found between age and change in MUAP size in patients with PPS (r=-0.215, p=0.147) or in controls (r=-0.243, p=0.472).

Variable	Ν	T0 ^a	T1ª	Change
Controls				
MUAP size (mV*ms)	11	1.59 (0.50)	1.43 (0.47)	-0.163 (0.55)
Force (Nm)	12	120.8 (32.9)	85.6 (37.1)	-35.2 (22.9) ^b
RMS amplitude (mV)	10	0.25 (0.05)	0.22 (0.10)	-0.03 (0.07)
LOI (%)	10	55.0 (11.9)	46.2 (15.0)	-8.8 (9.9) ^b
PPS, all				
MUAP size (mV*ms)	47	3.99 (2.08)	3.15 (1.85)	-0.81 (1.73) ^{b,c}
Force (Nm)	47	64.3 (33.8)	54.7 (32.6)	-9.6 (20.9) ^{b,c}
RMS amplitude (mV)	45	0.40 (0.25)	0.31 (0.15)	-0.09 (0.18) ^b
LOI (%)	45	36.5 (14.0)	35.4 (12.7)	-1.0 (12.8)
PPS, most severely affected muscles ^d				
MUAP size (mV*ms)	16	6.32 (1.77)	4.61 (2.34)	-1.71 (2.50) ^{b,c}
Force (Nm)	16	56.7 (35.9)	43.5 (29.0)	-13.2 (11.9) ^{b,c}
RMS amplitude (mV)	14	0.64 (0.26)	0.43 (0.11)	-0.21 (0.23) ^{b,c}
LOI (%)	14	39.3 (6.8)	35.8 (10.2)	-3.5 (10.3)

Table 2.1 Outcome measures for controls and patients with PPS, and separately for the patients with the most severely affected muscles

Abbreviations: MUAP size = motor unit action potential size; RMS = root mean squared; LOI = level of interference.

^a T0 and T1 indicate baseline and follow-up time points, respectively. All values are means (SD).

^b Significant change over time within a group (p<0.05),

^c Rate of change significantly different from the control group rate of change (p<0.05).

^d Top tercile initial MUAP size; i.e. MUAP sizes >4.2mV*ms at baseline.







Figure 2.3 Change in mean motor unit action potential (MUAP) size.

The change in mean MUAP size over 10 years in patients with PPS (open squares) and controls (filled triangles) is plotted relative to the initial mean MUAP size. Negative values indicate a decrease in the mean MUAP size.

At 60% MVC, patients with PPS had significantly higher RMS amplitudes and lower LOIs than controls at baseline (both p<0.001) (Table 2.1). Over 10 years, the initial RMS amplitude decreased by 22.7±45.3% in patients with PPS, while no change was found in controls (Table 2.1 and Figure 2.2). Conversely, the LOI was reduced by 15.9±18% in controls, but did not significantly change in patients with PPS.

Muscle strength

Over 10 years, patients with PPS showed a significant $15\pm33\%$ decrease in quadriceps strength (Table 2.1 and Figure 2.2). The controls had significantly greater strength than patients, both at baseline (p<0.001) and at follow-up (p=0.006), while they lost a significantly larger amount of strength (29±19%) than the patients with PPS (Table 2.1 and Figure 2.2). In patients with PPS there was no correlation between age and the rate strength decline (r=0.045, p=0.762), while in controls, age and loss of strength were significantly, strongly correlated (r=0.803, p=0.002).

Relationship between mean MU size decline and strength decline in PPS

In the PPS group, the 16 patients with the largest initial MUs, experienced the greatest declines in mean MUAP size (27%), RMS amplitude (32%), and strength (23%) (Table 2.1). All three independent variables, RMS amplitude, LOI and initial strength, were retained in the explanatory model for change in maximal strength (Table 2.2). Force at baseline was inversely related to change in force, indicating those with high initial strengths experienced the greatest declines. Changes in LOI and RMS amplitude were directly related to the change in force. Together, initial strength, change in RMS amplitude, and change in LOI accounted for 35% of the variability in changes in the strength of patients with PPS.

Table 2.2 Linear regression analysis for change in maximal strength in patients with PPS

Variable	Beta	Standardised Beta	Adjusted R ²
RMS amplitude change	36.6	0.315	0.184
Force at baseline	-0.23	-0.359	0.248
LOI change	0.57	0.344	0.345

Abbreviations: RMS = root mean squared; LOI = level of interference.

Discussion

This long-term longitudinal study provides neurophysiological evidence for the attrition of nerve endings in PPS and support for the hypothesis that denervation leads to strength decline. As hypothesised, patients with PPS lost both strength and MU size over 10 years, and the rate of decline in strength was related to the rate of decline in both MU size and number. In contrast to expectations, patients with PPS lost less strength than controls. The strength decline of controls was not accompanied by a reduction in MU size, indicating a different underlying mechanism.

As hypothesised, patients with PPS showed significant reductions in MU size over time. Both the area under the MUAP curve and the RMS amplitude of the raw signal revealed the same pattern in nearly identical proportions. These findings contrast those from macro-EMG studies, which reported no decline or increase in MU size at the group level.⁸⁻¹¹ In two of these studies, the small number of people with symptoms of PPS and the short follow-up duration could explain the lack of detection of a significant change.^{9,10} In the other studies, patients had contracted polio later in life, and not all patients were symptomatic.^{8,11} The MUs in those patients might therefore still have had residual capacity for continued axonal

sprouting to counteract denervation.^{5,6} In our sample of patients with PPS and proven quadriceps dysfunction, this residual capacity was insufficient, evidenced by the declines in MU size. This was particularly clear in those patients with the most severely affected muscles; i.e. those with greatly enlarged and therefore few MUs at baseline.²⁰

In contrast to many previous studies, we included only patients with PPS that showed symptomatic decline and neuromuscular transmission defects in a functionally important muscle group. Despite this homogenous sample, the rate of decline in muscle strength (15% over 10 years) was similar to that reported in previous studies that also included polio survivors without PPS (1 to 2.5% annually),²⁻⁴ confirming the slow progressive nature of PPS.

The finding that MU size did not change in the controls was in accordance with expectations and supported by data from cross-sectional studies, which suggested that MUs grow larger with increasing age, but not before 60 years of age.²¹⁻²³ Only three of our controls were over 60 years at baseline. Longitudinal studies of strength decline in healthy middle-aged subjects using isometric strength testing found a 1.4 to 3.4% annual loss in knee extension strength, in line with the 2.9% annual loss we observed.²⁴⁻²⁷ Proposed explanations for this sarcopenia include loss of whole MUs,^{21,23} and metabolic and endocrine changes leading to loss of contractile properties.^{25,26} The high positive correlation between age and rate of strength decline in our controls supported the theory that loss of strength was related to 'normal' aging.

The slower rate of strength decline in patients with PPS might indicate that their muscles suffer less from sarcopenia. It has been suggested that many age-related muscle changes may be the result of a sedentary lifestyle.^{28,29} In patients with PPS, a greater proportion of the muscle will be used during activities of daily life, because muscle mass is reduced.³⁰ This extra loading of the muscle during daily tasks could act as an exercise training stimulus and help maintain muscle strength, just as ageing athletes maintain higher strengths compared to their non-active peers.³¹ In addition, many patients with PPS have a predominance of type I muscle fibres,³⁰ while sarcopenia occurs primarily mainly in type II muscle fibres.³² Regardless of the underlying mechanism, the functional consequences of the loss of strength are most likely greater in patients with PPS, as they lack additional strength reserves.³³

The explanatory model for strength decline and the proportionality of MU size diminution and strength decline in those with the largest initial MUAPs supported the hypothesis that MU diminution contributed to the loss of strength in PPS. This finding substantiated previous incidental findings in a few muscles (n=2 and n=4, respectively) with very large initial motor units, which showed decreases in both MUAP size and strength.^{8,9} Apart from MU size, MU number is also an important determinant of muscle strength. Previous studies found ongoing loss of whole MUs in polio survivors.^{2,20} Although, in this study, the average group LOI did not decline over 10 years, it was retained in the explanatory model for strength change. This indicated that the individuals who lost a large amount of active MUs had a higher rate of strength decline than those who did not. The high degree of individual variability may explain why this factor was nevertheless retained in the model.

Our study has several limitations. We studied only the vastus lateralis muscle with EMG; however, the degree of damage from polio may vary between the four heads of the quadriceps that determine knee extension strength. We anticipate that a stronger relationship between MU characteristics and strength would have been found, had all four muscles been studied.

Surface EMG could potentially be more biased towards superficial MUs than needle EMG techniques. However, a study investigating the relationship between macro EMG and HDsEMG found very high positive correlations between MUAP sizes determined using these techniques.¹⁹ Also, the two techniques had almost the same relative ranges of MUAP parameters in each individual subject compared to the others.¹⁹ Surface EMG has the added advantage over needle EMG of being non-invasive and covering a larger section of the muscle. After 10 years, several uncontrollable factors may have changed that could be responsible for lowering the reproducibility of the HDsEMG measurements; for example, the amount of subcutaneous and intramuscular fat and the exact positioning of the grid. To minimise technical variability, all EMG measurements at baseline and follow-up were performed by the same technician, and all data was analysed according to a standard protocol by one researcher with the same software. Moreover, the newly used semi-automated decomposition programme increased objectivity, because the signal-to-noise threshold was determined mathematically, rather than visually; thus reducing assessor decisions.

LOI is an indicator of the number of active MUs, but it can also be affected by MU firing synchronisation and firing frequency. Thus, the LOI findings were not directly comparable to the MU number estimations from other studies.^{2,20,34}

The small number of control subjects did not allow subgroup analyses or linear regression analysis. This limited the avenues that could be explored; nevertheless, our findings were relevant, because, to our knowledge, this study was the first to include long-term, longitudinal MU size measurements in healthy controls.

Some particular strengths of this study were the long follow-up time, low drop-out rate, and inclusion of individuals with proven dysfunction in the large, functionally important muscle under investigation. Moreover, the used surface EMG technique is non-invasive and this study showed that long follow-up studies are realisable. Hence this technique could be potentially useful for determining changes in MU-size in follow-up studies in patients with other neuromuscular and motor neuron diseases.

Conclusion

This was the first study to demonstrate that MU size indeed declined in patients with PPS, that the decline was greatest in the muscles with the fewest remaining units, and that the rate of denervation was related to the rate of strength decline. These findings support the hypothesis that enlarged MUs cannot be sustained indefinitely, and that excess degeneration of distal axons contributes to the strength decline in PPS. Taken together with findings from previous studies that showed an ongoing loss in whole motor units, this study provided evidence for a complex model of the pathophysiology of PPS progression. Future research should focus on underlying causes of MU loss and attenuation, because slowing this process could reduce or postpone the loss of strength in PPS, and potentially, in other motor neuron disorders.

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Chapter 3

Quantitative muscle ultrasound and quadriceps strength in patients with post-polio syndrome

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Abstract

Introduction: We investigated whether muscle ultrasound can distinguish muscles affected by post-polio syndrome (PPS) from healthy muscles and whether severity of ultrasound abnormalities is associated with muscle strength.

Methods: Echo intensity, muscle thickness, and isometric strength of the quadriceps muscles were measured in 48 patients with PPS and 12 healthy controls.

Results: Patients with PPS had significantly higher echo intensity and lower muscle thickness than healthy controls. In patients, both echo intensity and muscle thickness were associated independently with muscle strength. A combined measure of echo intensity and muscle thickness was more strongly related to muscle strength than either parameter alone.

Conclusion: Quantitative ultrasound distinguishes healthy muscles from those affected by PPS, and measures of muscle quality and quantity are associated with muscle strength. Hence, ultrasound could be a useful tool for assessing disease severity and monitoring changes resulting from disease progression or clinical intervention in patients with PPS.
Introduction

Post-polio syndrome (PPS) is a neuromuscular disease (NMD) characterized by slowly progressive loss of muscle strength and endurance.¹ Muscles typically function with a decreased number of motor units of increased size due to reinnervation following acute polio.²⁻⁷ There is often extensive fibrosis and steatosis of muscle fibers, which disrupts the normal muscle architecture.^{6,8-10} Any skeletal muscle can be involved, and the severity of involvement is highly variable. Clinical involvement and disease progression in PPS are usually assessed with functional tests, such as muscle strength measurements.¹¹ The scale used most frequently to assess muscle weakness in clinical practice, the MRC-scale, has limitations in that it is non-linear, has little discriminative ability, and scoring has a ceiling effect.^{12,13} Furthermore, the sensitivity of this scale to changes in muscle strength is rather low,^{12,13} and reliability of strength tests in PPS can be impeded by frequent and variable symptoms, such as muscle and joint pain and fatigue.^{1,14-16}

Quantitative muscle ultrasound is a potential alternative for assessment of disease severity and progression in PPS. The main findings in NMDs are increased echo intensity, which reflects increased infiltration of fat or fibrous tissue, and decreased muscle thickness, which indicates atrophy.¹⁷⁻²¹ Muscle ultrasound is performed on relaxed muscles and, unlike muscle strength testing, it is not hindered by common symptoms such as muscle and joint pain.²² Additional advantages are its high discriminative ability, low cost, speed, and non-invasive nature.^{19,22} Whether or not the structural abnormalities quantified with ultrasound also reflect muscle function, e.g. strength, in NMDs is not yet clear. Only a few studies so far have investigated associations between quantitative ultrasound parameters and muscle strength in NMDs, and these have reported ambiguous associations, depending on the muscles tested, patients studied, and methods used.^{18,23-25}

In this study, we sought to determine whether muscle ultrasound can distinguish muscles of patients with PPS from those of healthy controls and whether the severity of ultrasound abnormalities is related to muscle strength in this disorder.

Methods

Participants

The cohort has been described in detail elsewhere.^{2,4,26} The cohort consisted of 48 adults with PPS and 12 healthy controls in the same age range who had completed strength measurements as part of a longitudinal study and agreed to participate in an additional one-time muscle ultrasound measurement at follow-up in 2010.² All individuals with PPS had symptoms of post-poliomyelitis muscle dysfunction in at least 1 quadriceps muscle.¹ The patients also showed evidence of neuromuscular transmission defects on a single-fiber EMG (in 2000), which is indicative of ongoing denervation and reinnervation. They had no important comorbidities. In this study, the follow-up data (2010) were used. All participants provided written informed consent, and the study was approved by the institutional Medical Ethics Committee.

Study design and measurements

In this cross-sectional study, all participants underwent unilateral strength and ultrasound measurements of the strongest symptomatic quadriceps muscle. In healthy controls, the strongest leg was chosen unless unilateral joint or muscle problems were present.

Muscle ultrasound

All ultrasound measurements were performed by an experienced clinical neurophysiology technician, with a Zonare z.one ultrasound machine (Zonare z.one, Medical Systems, Inc., Mountain View, CA, USA). The transducer was an L10-5 linear array set at 8.5 MHz, and the system settings were as follows: dynamic range, 60; gain, 78; and depth, 4 cm. Throughout the measurements participants remained supine, with the legs extended and muscles relaxed. All scans were made in the transverse plane, with the transducer at the standard location for the muscle belly of the vastus lateralis muscle: two-thirds of the way along the line from the anterior superior iliac spine to the superior aspect of the patella.²⁷ Three digital images were obtained in each participant from consecutive measurements at the standard location and were stored as DICOM files for further offline analysis of echo intensity and muscle thickness.

Mean muscle echo intensity was quantified using computer assisted gray-scale analysis in a custom-made image analysis software program (QUMIA). First, a region of interest was

selected by hand from each muscle image so that it included as much of the vastus lateralis muscle cross-sectional area as possible without the surrounding fascia or bone tissue. Screen image edges were avoided, as these are prone to artifact. The mean echo intensity for this region was then calculated as the average value of the pixels that were expressed as a value between 0 (black) and 255 (white). For each participant, the mean echo intensity of each of the 3 consecutive measurements was averaged in order to minimize measurement variability.

Muscle thickness was measured with electronic calipers according to a standard protocol also used in the collection of normative data.²⁷ Because the exact outlines of the vastus lateralis muscle can be difficult to determine in case of severe muscle pathology, the underlying femoral bone was chosen as a reference point. The resulting muscle thickness was thus a combination of the thickness of the vastus lateralis and vastus intermedius muscles.

Strength

Peak knee extension strength (Nm) was defined as the strongest of 3 isometric maximal voluntary contractions performed on a hard surfaced, fixed chair dynamometer with knee and hip flexed at 90deg. The lower leg was strapped to a lever arm containing force transducers, and visual feedback was provided by displaying the attained force on a screen.²

Data analysis

Outcome measures were echo intensity (EI), muscle thickness (MT), echo intensity-muscle thickness index (EI-MT index), and knee extension strength (Nm). Muscle thickness (cm) was transformed to a z-score using normative data acquired in a previous study from 54 volunteers aged 21–86 years.²⁷ In this way, data could be corrected for age and gender, which are known to influence muscle thickness. Because muscle quality and muscle quantity were both expected to be important determinants for strength, we created a combined measure. Since echo intensity increases with decreasing muscle quality, while muscle thickness decreases with decreasing muscle quantity the 2 measures should have an opposite relationship to strength. An EI-MT index was calculated according to the following formula:

EI-MT Index =
$$\frac{\text{mean healthy control EI}}{\text{measured EI}} \times \text{measured MT}$$

Hence, a small value of EI-MT index indicates poor muscle quality and /or quantity.

Normally distributed data were presented as mean \pm standard deviation, and univariate correlations were tested with the Pearson correlation coefficient. For non-normally distributed data, medians and interquartile ranges were determined. Due to expected unequal variances between the control and PPS groups, group differences were tested with Mann-Whitney U. Multivariate analysis was done using forward stepwise binary linear regression to assess the role of MT and EI in knee extension strength of patients with PPS. Significance was set at *p*<0.05.

Results

Participants

The mean ages were similar in the PPS (63 ± 8) and control groups (59 ± 14 , p=0.260), and both groups had slightly more women than men (both 67%). At the time of the polio infection, the median age was 2.5 [1–4] years; the average time since polio was 60 ± 9 years.

Representative ultrasound images of the vastus lateralis of a healthy control and a patient with PPS can be seen in Figure 3.1. All outcome measures differed significantly between



Figure 3.1 Ultrasound images of the vastus lateralis of (A) a healthy control and (B) a patient with PPS.

The solid white line indicates the area of the vastus lateralis that was used to calculate echo intensity, and the dotted white line indicates the muscle thickness, as measured from the outer edge of the vastus lateralis to the femoral bone (i.e. including the vastus intermedius). The muscle of the patient with PPS is much thinner (atrophic) and whiter (echo intense) compared with that of the healthy control.

PPS patients and healthy controls (Table 3.1). Specifically, patients had significantly higher EI, lower MT, and lower strength than healthy controls (Table 3.1). The average muscle thickness of patients was 1 z-score under reference values from a large group of healthy controls, corrected for age and gender.²⁷ The lower EI-MT index in patients indicated poor muscle quality and/or quantity compared to controls. EI and MT were correlated moderately

Variables	PPS (n=48)	Controls (n=12)	p-values C-P
Ultrasound			
EI [0–255]	60.5 (15.9)	33.3 (16.0)	< 0.001**
MT (cm)	2.60 (0.67)	3.19 (0.53)	0.013*
EI-MT index	1.57 (0.67)	3.96 (2.04)	< 0.001**
z-score MT	-1.02 (2.0)	0.53 (1.0)	0.007**
Strength (Nm)	55.7 (33.0)	85.6 (37.1)	0.015*

Table 3.1 Comparison of ultrasound parameters and strength between patients with PPS and controls

Abbreviations: EI = echo intensity; MT = muscle thickness; PPS = post-polio syndrome; C-P = controls versus patients. Values are means (standard deviations).

* *p*<0.05 and ** *p*<0.01 for patients with PPS versus healthy controls, Mann-Whitney U.



Figure 3.2 The relationship between echo intensity and muscle thickness.

Muscle thickness (cm)

in patients with PPS (r=-0.321, p=0.026) and not in healthy controls (r=-0.099, p=0.760), although the relationship in both groups followed the same trend (Figure 3.2).

In PPS patients, strength was associated significantly with both EI and MT (Table 3.2). Together these variables explained 30.7% of variability in strength (Table 3.3). The combined EI-MT index correlated more strongly with strength than either EI or MT alone (Table 3.2). In controls, strength correlated significantly with muscle thickness and EI-MT index, but the association with EI did not reach significance (Table 3.2). Visually, the relationship between echo parameters and strength seemed similar for controls and PPS patients (Figure 3.3). However, in controls with very low EIs (<30) there appeared to be little relationship to strength (Figure 3.3A). Similarly, in PPS patients with very low strengths (<30 Nm), there appeared to be little relationship with MT (Figure 3.3B).

				,,
	PPS (n=48)	PPS (n=48)		2)
Variable	Strength [†]	<i>p</i> -value	Strength ^a	<i>p</i> -value
EI	-0.463	0.001**	-0.573	0.052
MT	0.480	0.001**	0.600	0.039*
El-MT index	0.607	< 0.001***	0.677	0.016*

Table 3.2 Correlations of strength with ultrasound parameters for PPS patients and healthy controls

Abbreviations: EI = echo intensity; MT = muscle thickness; PPS = post-polio syndrome.

Correlations significant at p<0.05 and p<0.01.

^a Values are Pearson correlation coefficients (r).

Table 3.3	Linear regression analysis for maximal strength in patients with PPS	
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Variable	Beta	Standardized Beta	Adjusted R ²
MT	18.3	0.370	0.214
EI	-0.71	-0.344	0.307

Abbreviations: EI = echo intensity; MT = muscle thickness; PPS = post-polio syndrome.

Discussion

In this study, we established that ultrasound can distinguish muscles of PPS patients from those of healthy controls. We also demonstrated a clear relationship between the ultrasound and strength parameters in PPS patients. Hence, EI and MT are potentially useful indicators of disease severity and may capture changes resulting from disease progression or intervention in PPS patients, both in trials and clinical practice.



Figure 3.3 Correlations between strength and (A) echo intensity, (B) muscle thickness, and (C) EI-MT index.

Previous studies found increased EI in patients with a variety of NMDs and connective tissue disorders, such as amyotrophic lateral sclerosis (ALS),²⁸ Marfan syndrome,²⁹ Ehlers-Danlos syndrome,³⁰ muscular dystrophies, inflammatory and congenital myopathies, and spinal muscular atrophy (SMA),²⁵ compared to healthy controls.²² In addition, reduced MT was demonstrated in neurogenic NMDs.²² Similarly in this study, PPS patients had a substantially higher EI and lower MT of the vastus lateralis muscle than healthy controls. Thus ultrasound reflected the expected changes based on known pathological changes in PPS.^{6,8-10} The differences between PPS and healthy controls served as a proof of principle; ultrasound was sufficiently sensitive to distinguish between muscles affected by PPS and healthy muscles.

In healthy muscles, strength is correlated highly with measures of muscle quantity.^{19,31,32} In this study we also found a positive relationship between muscle strength and MT in healthy controls, as was demonstrated previously among older women³³ and children.³⁴ However, there is also evidence that changes in muscle quantity do not explain changes in strength entirely, as the amount of force per unit of muscle size may increase after training, decrease as a result of sarcopenia, and differ between genders.³² How it is affected by muscle disease is not known. Proposed explanations for this variation include differences or changes in neural stimulation (activation) and muscle quality.^{31,32} In support of this theory, we found that the relationship with strength improved when information about muscle quality (EI) was taken into account alongside MT (EI-MT index). Visually, a linear relationship between EI and strength was only observed in those with higher EIs (i.e. poorer muscle quality) (Figure 3.3A). Although conclusions must be tentative because of the small size of our control group, this implies that strength in healthy muscles is represented adequately by MT alone until muscle quality decreases under (i.e. EI increases above) a certain threshold.

In PPS patients there was also a clear positive relationship between strength and MT. However, at very low strengths, the relationship was less convincing (Figure 3.3B), unless EI was also taken into account (Figure 3.3C). Indeed, both EI and MT contributed equally to the model for muscle strength. These results imply that in diseased muscles, muscle quantity and quality are both necessary for accurate prediction of muscle strength. Previous studies in other NMDs (i.e. ALS, SMA, and non-dystrophic myotonia) reported no, weak, and moderate correlations between strength and EI, and strength and MT.²³⁻²⁵ These varying results may be explained by differences in the types of muscles tested, in disease-specific characteristics, and especially in the types of strength measurements used, i.e. manual muscle testing²³ and hand-held dynamometry,^{24,25} rather than isometric strength assessment with fixed dynamometry.

We expected the process of atrophy and fibrosis or fatty infiltration of muscle fibers would occur concomitantly in muscles of PPS patients, as both processes can result from denervation.¹⁹ However, the relationship we found between EI and MT was only moderate, and the variability within the group was large (Figure 3.2). When only a small amount of functional muscle tissue remains, this tissue will be used at relatively higher loads compared to normal muscle during activities of daily life. As was also hypothesized elsewhere, this increased use might act as a training stimulus and help preserve muscle quality.² This could explain the finding of good EIs in some individuals with severe atrophy (loss of whole muscle segments, sparing of others) and hypertrophy in some with very poor EIs (remaining healthy hypertrophic fibers interspersed with fatty infiltration or fibrotic tissue) (Figure 3.2). Conversely, relative disuse of muscles in grossly impaired limbs could also lead to atrophy with or without severe loss of muscle quality. The concurrent existence of these conflicting processes might explain the high degree of variability in the relationship between EI and MT in patients with PPS.

Our findings support the use of ultrasound to help establish clinical disease severity in polio survivors. Currently, the NRH-limb classification system is used for this, which involves clinical strength tests and invasive needle EMG.¹¹ A screening of important skeletal muscles using ultrasound would have multiple advantages over these tests due to its speed, reliability, low cost, and non-invasive character.^{19,22} Ideally, a set of functionally important muscles as well as symptomatic muscles should be assessed in such a screening. Normative data are already available for 12 important muscle groups.^{27,35} Another clinical application of muscle ultrasound may be as a monitoring tool to track progressive loss of muscle mass. Lee et al., showed a moderate correlation between the significant decline in biceps MT and grip strength over 6 months in ALS patients,³⁶ while Arts et al., found no correlation between changes in ultrasound parameters and strength of 6 muscles over the same period.²³ In the latter study, strength was measured with MRC-scores determined through manual muscle testing and was therefore subject to limited sensitivity.^{12,13} Further longitudinal research using objective strength measures of the same muscle being investigated with ultrasound is necessary to determine whether or not ultrasound has the ability to accurately assess change in muscle strength over time.

This study had some potential limitations. First, we studied only the vastus lateralis muscle, while the degree of damage from polio may vary between the 4 heads of the quadriceps. We anticipate that a stronger relationship between ultrasound parameters and strength would have been found, had all 4 heads been studied. Studying additional multiple lower

limb muscles bilaterally would moreover allow a more comprehensive comparison between ultrasound parameters and strength and potentially also with other functional parameters such as walking ability. The correlations between muscle strength and ultrasound parameters in this study might have been further affected negatively by variability in (voluntary) muscle activation due to symptoms of fatigue and pain.

Second, we used a linear dimension to assess muscle quantity (i.e. MT) instead of crosssectional area (CSA), which has been studied more extensively in relation to muscle strength.^{31,32} Muscle thickness has been shown to correlate well with CSA.³⁷ Moreover, correlations between strength and converted muscle thickness values (Π^*r^2 or MT²) in our sample yielded very comparable results to those found using MT directly (data not shown).

Last, conversion of EI values to z-scores (i.e. correction for age and gender) was not possible because of the small size of our control group and use of a new ultrasound machine with settings different from those used for normative data elsewhere.²⁷ However, the z-scores for MT found in our control group were very similar to the normative data, suggesting that our control group was most likely a representative sample.³⁵

In this study, we did not include any dynamic ultrasound measures such as the degree of thickening on contraction of the muscle and quantification of muscle blood flow.

Muscles of patients with PPS might show less thickening during contraction than those of healthy controls, as was previously found in myositis.³⁸ It would be interesting to investigate the relationship between this measure of reduced muscle function and the measures of muscle quality (EI) and quantity (MT) described in this study. In healthy patients, increased muscle blood flow after even small amounts of exercise has been shown to contribute to measured muscle volume, but little is known about these changes in NMDs.¹⁹ Dynamic ultrasound measurements are thus a potentially interesting addition to future muscle ultrasound research in PPS.

Conclusion

Muscle ultrasound can distinguish diseased from healthy muscles by measurement of muscle quantity and quality. Both ultrasound parameters, EI and MT, are related to muscle strength. These characteristics mean ultrasound shows promise as a diagnostic tool for assessing clinical disease severity in PPS patients, particularly those who have complaints that limit strength tests. We propose the use of a combined measure of EI and MT, rather than the individual parameters. Ultrasound parameters might also be potentially useful outcomes for disease progression in PPS. Future research should focus on the sensitivity of ultrasound to longitudinal changes in patients with progressive declines in muscle function.

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Chapter 4

Elevated plasma inflammatory mediators in postpolio syndrome: no association with long-term functional decline

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Abstract

Introduction: A key feature of post-polio syndrome (PPS) is progressive loss of muscle strength. In other chronic diseases systemic inflammation has been linked to muscle wasting.

Methods: Plasma levels of 12 pro-inflammatory mediators (IFN- γ , IL-1 α , IL-1 β , IL-6, IL-8, leptin and TNF- α), anti-inflammatory mediators (IL-1RA and IL-10), and immunemodulatory mediators (IL-13, IL-17A and IL-18) were investigated in 45 PPS-patients with symptomatic quadriceps dysfunction and 18 healthy controls. For PPS-patients these levels were compared to the change in motor unit size, isometric quadriceps strength and walking capacity over 10 years.

Results: Plasma TNF- α , IL-6, IL-8, and leptin levels were significantly increased in PPSpatients compared to healthy controls. There was however no association between these raised systemic levels of inflammatory mediators and long-term decline in quadriceps strength or other clinical parameters.

Conclusion: There is evidence for systemic inflammation in PPS, yet the relationship with clinical deterioration remains tenuous.

Introduction

Post-polio syndrome (PPS) is a neuromuscular disease characterised by slow progressive loss of muscle strength and increased muscle fatigability reflecting ongoing motor unit loss and degeneration.¹⁻⁴ Furthermore, PPS-patients frequently suffer from complaints such as fatigue and generalised pain.^{5,6} The cause of these motor unit changes and associated morbidities years after the acute infection is not well understood. It has been proposed that both chronic systemic and localised inflammatory processes are involved.⁷

Studies to date have found evidence of local inflammation and immunological responses in the central nervous system,⁸⁻¹⁴ muscle^{15,16} and vascular system^{17,18} of PPS-patients. Also, the presence of inflammatory markers and mediators in peripheral blood of PPS-patients indicates systemic immunological activation.^{12-14,19,20} The reasons for this immune activation and the connection between local or systemic inflammation and clinical manifestations of the disease however remain unresolved. There is some evidence for a possible relationship of inflammatory mediator levels with pain and with self-reported physical functioning, but none with muscle strength, fatigue or walking capacity.^{7,12,19-21} In studies examining mRNA expression of major pro-inflammatory mediators in central nervous system, $TNF-\alpha$ and IFN-y expression declines after intravenous immunoglobulin treatment.¹³ However, the reported effects of this immunoglobulin treatment on symptoms vary, with a meta-analysis revealing inconsistent effects on muscle strength and no effect on pain or activity limitations.⁴ Lack of correlations and inconsistent results in these studies might be explained by the great variation in mediators and substrates studied, clinical tests used and control groups included in each study.^{4,7,12,13,19-21} No study so far has evaluated a large selection of inflammatory mediators, the relationship between inflammatory mediator levels and motor unit changes, or the relationship between inflammatory mediator levels and the *rate* of clinical decline.

In this study we aimed to verify evidence for systemic inflammation in PPS-patients using a panel consisting of 3 different groups of mediators: (i) pro-inflammatory, (ii) antiinflammatory, and (iii) immune-modulatory. This broad panel included key mediators representative of specific inflammatory pathways allowing analysis of the pathways potentially involved in the immune response in PPS. Furthermore, we aimed to determine whether patients with evidence of inflammation were also those with the highest rate of clinical deterioration, i.e. a faster rate of decline in quadriceps strength, motor unit size, or physical mobility over the previous 10 years.

Methods

Subjects

The PPS-cohort has been described in detail elsewhere.^{2,22} Sixty-six adults with PPS that had completed baseline measurements in a randomized controlled trial of pyridostygmine between 1999 and 2001, were invited to participate in the present study, 10 years later.²³ At baseline, all individuals had PPS, with symptoms of post-poliomyelitis muscle dysfunction in either or both quadriceps muscles.¹ They also showed evidence of neuromuscular transmission defects on single-fibre EMG, indicative of ongoing denervation and reinnervation, and had no important comorbidities. Detailed in- and exclusion criteria are described elsewhere.²³ New exclusion criteria were the presence of any newly developed disease that affected voluntary control of the muscles, immunological diseases and the use of immune-regulatory medication. Eighteen healthy controls, gender-matched and in the same age range as the PPS-patients, were selected from a larger pool of healthy volunteers who donated blood to the hospital laboratory in 2010 for reference value determination. The healthy controls were not subjected to any other clinical tests.

All participants provided written informed consent, and the institutions' Medical Ethics Committee approved the study.

Study design and measurements

In this cohort study, all PPS participants underwent a standardized assessment of functioning on two separate days, in most cases within two weeks and never more than 3 months apart. This assessment was performed in the same way at baseline and follow-up. Day 1 encompassed an intake and physical examination, completion of questionnaires and a walking capacity test. On day 2, isometric strength measurements and high-density surface EMG measurements were performed on the strongest symptomatic quadriceps muscle as measured at baseline. Longitudinal changes in strength and motor unit size (MU-size) have been reported elsewhere.^{2,22} Peripheral blood samples for haematological and inflammatory mediator analysis were taken on day 1 -before any activity measurements- at follow-up only. Healthy controls underwent venepuncture only.

Analyses of inflammatory mediators

Peripheral blood was collected from PPS participants and healthy controls in EDTA to prevent clotting. First, 200 µL of each blood sample was removed for haematological analysis of leukocyte counts and differentiation. Then, the remainder of the sample was centrifuged for 10 minutes at 1700xg and plasma was aliquotted and stored at -80° Celsius until analysis. This procedure was completed within 1h30min after venepuncture to limit bias by prolonged incubation with blood cells. A panel of twelve mediators were determined using luminex (Bioplex, BioRad, Veenendaal, the Netherlands) according to the manufacturer's instructions. This panel was chosen to distinguish mediators active in different immune pathways. The panel consisted of: (i) pro-inflammatory mediators: interferon- γ (IFN- γ), IL-1 α , IL-1 β , IL-6, IL-8, leptin and tumor necrosis factor- α (TNF- α); (ii) anti-inflammatory mediators: IL-1RA and IL-10; and (iii) immune-modulatory mediators: IL-13, IL-17A and IL-18. The stored plasma samples from PPS-patients and healthy controls were analysed in parallel.

Clinical measures

MU-size: High-density surface EMG was used to estimate MU-size. The measurement and analysis protocol has been described extensively previously.^{2,24} Briefly, a rectangular electrode grid composed of 130 gold-coated electrodes (electrode diameter: 1.5 mm; interelectrode distance: 5 mm), was placed over the vastus lateralis muscle, such that 10 columns with 13 electrodes each were positioned parallel to the muscle fibres. A reference electrode was placed on the patella. Monopolar signals were stored for offline analysis after the required amplification and filtering procedures.² Single motor unit action potentials (MUAPs) were extracted from bipolar EMG recordings of five, 30-s contractions between 5% and 20% of peak knee extension strength using a semi-automated software programme.²⁵ MUAP-size of each unique MUAP was then calculated from the area under the curve of 50 ms of the monopolar signal from the electrode nearest to the endplate zone. The mean MUAP-size was then calculated for each patient at baseline and follow-up.

Quadriceps strength: Peak knee extension strength (Nm) was defined as the strongest of three isometric maximal voluntary contractions performed on a hard surfaced fixed chair dynamometer with knee and hip flexed at 90 deg.

Walking capacity: The distance walked (m) in two minutes at a comfortable pace on a standardised 50 m oval circuit was recorded.²⁶ Participants used the same assistive walking devices they used in daily life.

Statistics/data analysis

The main outcome measures were circulating levels of the 12 measured mediators (i.e. IFN-γ, IL-1α, IL-1β, IL-1RA, IL-6, IL-8, IL-10, IL-13, IL-17A, IL-18, TNF-α and leptin) (pg/ml), mean MUAP size (mV*ms), knee extension strength (Nm) and walking capacity (m). Means with standard deviations (SD), medians with interquartile range [IQR], and percentages were used to describe the population. For levels of inflammatory mediators that were below the detection level, we used half the value of the lower limit of detection in the statistical analyses. Differences between levels of inflammatory mediators of patients and controls were tested non-parametrically using Mann-Whitney U test because of unequal variances between the groups. Interrelations between levels of different mediators, included to investigate which pathways might be active in PPS, were tested using Pearson correlations. Interrelations between levels of mediators and leukocyte cell counts and of mediators and BMI were also tested using Pearson correlations. These assessments were included to check if increased numbers of white blood cells and/or fat cells could underlie abnormal levels of inflammatory mediators in this group. Associations between mediator levels and clinical parameters were analysed by comparing the rate of change in clinical parameters of those with mediator levels above and below the p75 control value for that mediator (Mann-Whitney U). Only those mediators that were significantly increased in PPS-patients were analysed in this way. Statistical analysis was performed with the SPSS statistical software package (version 20.0.0.1). Significance was set at p = 0.05.

Results

Subjects

Forty-six patients with PPS agreed to participate with the inflammatory mediator measurements. Non-participants were untraceable (n=6), deceased (n=2), unwilling/unable (n=6), or excluded for: (i) co-morbidities that may have affected the quadriceps under investigation (n=4), (ii) immunological disease (i.e. chronic lymphocytic leukaemia) (n=1), and (iii) use of anti-inflammatory drug prednisone (n=1).

Analyses of plasma samples were completed for all 18 healthy controls and 45 PPS-patients. Due to clotting of the blood sample, inflammatory mediator analysis was not reliable for the remaining PPS-participant. Incomplete data on clinical parameters was obtained for 3 patients due to non-participation on day 2 of the measurements (n=2) and non-compliance with the measurement protocol (n=1).

In 2000, age was similar for controls and PPS-patients and both groups had slightly more women than men (Table 4.1). Other baseline characteristics for PPS-patients are given in Table 4.1.

Inflammatory mediator levels and correlations

Levels of IL-6, IL-8, TNF- α and Leptin were significantly increased for PPS-patients compared to healthy controls (Table 4.2). Using the p75 of healthy controls as a cut-off value, 69% of patients had elevated leptin, 56% elevated TNF- α , 47% elevated IL-8 and 38%

	PPS-patients (n=45 ^a)	Controls (n=18)	<i>p</i> -value
Age, years	51±8	49±6	0.178
Female gender, % (n)	64 (29)	67 (12)	0.870
Age at time of polio, years	2 [1–4]	-	-
Time since polio, years	48 ±9	-	-
BMI, kg/m²	26 ± 5	-	-
MU-size, mV*ms	3.2 [2.5–4.8]	-	-
Strength, Nm	64 [40–87]	-	-
Distance walked, m	128 [102–140]	-	-

Table 4.1 Baseline characteristics PPS-patients, 2000

Abbreviations: MU-size: Motor-unit size.

Values are means±SD, % (n) and medians [IQR]; a n=42 for MU-size, strength, walking capacity data.

	PPS (n=45) Concentrations (pg/ml)	Controls (n=18) Concentrations (pg/ml)	<i>p</i> -value
IL-1ra	980.6 [747.3–1385.9]	834.9 [556.2–995.1]	0.075
IL-6	3.7 [1.8–5.8]	1.8 [0.6–4.5]	0.023*
IL-8	31.7 [24.1–48.3]	22.7 [17.6–32.2]	0.035*
IL-10	6.2 [3.8–9.0]	4.2 [3.1–8.7]	0.235
IL-13	4.7 [2.8–8.0]	2.7 [0.9–7.8]	0.071
IL-17A	31.6 [16.3–55.3]	20.2 [9.4–30.2]	0.059
TNF-α	18.2 [10.3–28.9]	12.2 [6.5–17.5]	0.048*
IL-18	43.1 [31.6–54.5]	36.4 [29.5–47.1]	0.221
Leptin	2111.0 [1088.7–3603.7]	931.2 [617.0–1244.1]	0.001**

Table 4.2 Median inflammatory mediator levels for PPS-patients and healthy controls

Values are median [IQR]; * Significance set at *p*<0.05, tested with Mann-Whitney U. ** *p*<0.001.

elevated IL-6 levels. IL-17A and IL-1RA were not significantly raised for the group as a whole (p<0.075), yet 55% and 46% patients, respectively had levels above the p75 of controls. IL-1 α , IL-1 β and IFN- γ were below the detection level for both controls and PPS-patients (i.e. <2.16, <1.96 and <40 pg/ml, respectively). The remaining inflammatory mediators (IL-10, IL-18 and IL-13) did not differ significantly between the groups and only a small number of individuals had values above the p75 of controls for these mediators. Individual variation within the PPS group was large, but almost all patients (96%) had elevated levels of at least one inflammatory mediator (compared to 66% of controls) and half (51%) had elevated levels of 4 or more inflammatory mediators (compared to 22% of controls).

The levels of most mediators were strongly interrelated as can be seen in Table 4.3. Only leptin and IL-18 were not or weakly correlated with other inflammatory mediators. BMI was significantly and strongly correlated to leptin levels only (R=0.715, $p \le 0.001$). Leukocytes were minimally reduced in 1 participant and elevated in none. There were no correlations between mediator and leukocyte concentrations.

	IL-6	IL-8	IL-17A	TNF-α	Leptin	IL-1ra	IL-10	IL-13	IL-18
IL-6	1								
IL-8	0.755**	1							
IL-17A	0.605**	0,823**	1						
TNF-α	0.836**	0.569**	0.482**	1					
Leptin	-0.212	-0.261	-0.264	-0.246	1				
IL-1ra	0.866**	0.826**	0.665**	0.821**	-0.285*	1			
IL-10	0.728**	0.920**	0.745**	0.584**	-0.309*	0.830**	1		
IL-13	0.620**	0.852**	0.880**	0.442**	-0.279	0.661**	0.864**	1	
IL-18	0.269	0.288*	0.315*	0.061	-0.111	0.199	0.309*	0.354*	1

Table 4.3 Correlations between inflammatory mediators (PPS only, n=45)

* Significant at p<0.05, ** p<0.001. Values represent Pearson's r correlation coefficients.

Correlations with IL-1 β , IFN- γ en IL-1 α are not provided because of the low number of patients with detectable values (3, 4, and 7 patients respectively).

Relationship change clinical parameters and inflammatory mediator levels in PPS-patients

The group changes over 10 years in the clinical parameters have been reported more extensively elsewhere.²² Average MU-size, strength and walking capacity declined significantly over 10 years, by 21, 15 and 5%, respectively and individual variability was high. There were no significant differences between the 10 year changes in clinical parameters for

those with elevated and those with normal mediator levels of IL-6, IL-8, TNF- α or leptin (Table 4.4). Figure 4.1 further illustrates the lack of association between clinical parameters and mediator levels, using TNF- α and muscle strength as an example. Also, there were no significant differences in clinical parameters between those people with elevated levels of 4 or more different inflammatory mediators and those without (Table 4.4).

	Elevated mediator concentrations	Normal mediator concentrations	<i>p</i> -value
Leptin Δ MU-size (mV*ms) Δ Strength (Nm) Δ Walking capacity (m)	n=28 -0.4 [-1.2–0.2] -8 [-23–3] -5 [-12–4]	n=14 -0.5 [-1.7–0.4] -10 [-23–0] -6 [-30–8]	0.802 0.906 0.589
TNF-α Δ MU-size (mV*ms) Δ Strength (Nm) Δ Walking capacity (m)	n=24 -0.2 [-1.0–0.2] -5 [-19–2] -5 [-21–4]	n=18 -0.9 [-2.0–0.3] -17 [-29–0] -4 [-14–10]	0.204 0.155 0.542
IL-6 Δ MU-size (mV*ms) Δ Strength (Nm) Δ Walking capacity (m)	N=16 -0.2 [-0.8–0] -5 [-22–2] -5 [-21–2]	N=26 -0.9 [-1.8–0.3] -15 [-23–2] -6 [-14–6]	0.422 0.437 0.623
IL-8 Δ MU-size (mV*ms) Δ Strength (Nm) Δ Walking capacity (m)	N=20 -0.3 [-1.2–0.05] -5 [-17–3] -5 [-23–4]	N=22 -0.7 [-1.8–0.4] -16 [-27–-0.8] -6 [-13–7]	0.840 0.182 0.513
≥4 inflammatory mediators Δ MU-size (mV*ms) Δ Strength (Nm) Δ Walking capacity (m)	N=22 -0.2 [-1.3–0.1] -5 [-17–3] -8 [-23–3]	N=20 -0.9 [-1.6–0.5] -17 [-27–-2] -1 [-10–8]	0.920 0.107 0.137

 Table 4.4
 Comparison between changes in clinical parameters for PPS-patients with elevated mediator

 levels (>p75 of controls) and those within the normal range

Values are median change over 10 years [IQR]; P-values signify differences between groups of patients with elevated and normal mediators, tested with Mann-Whitney U.

Discussion

This study provides further evidence for systemic inflammation in PPS patients and suggests the involvement of certain inflammatory pathways. Despite clearly elevated levels of inflammatory mediators, we found no evidence to suggest that those patients with systemic inflammation are also those with the highest rate of long-term clinical deterioration.

Our findings of increased levels of TNF- α , IL-6, IL-8 and leptin in plasma partially confirm those of a previous study, which found increased TNF- α , IL-6 and leptin in *serum* of PPS



Figure 4.1 Plasma TNF-α levels in 2010 versus change in muscle strength over 10 years for PPS-patients (n=43).

Horizontal line is at P75 for controls, i.e. 17.5 pg/ml.

patients as compared to healthy controls using a similar technique.¹⁹ The findings oppose those from another study, which did not find elevated TNF- α in serum of PPS patients and did not report the outcomes for other inflammatory mediators.¹² This contradiction between studies might be explained by the differences in the immunoassay used or in the included reference group (matched healthy controls *versus* neurological patients). Other studies investigated expression of inflammatory mediator mRNA in circulating mononuclear cells in PPS-patients and varyingly found no increases of any mRNA,¹³ increased expression of TNF- α mRNA¹⁴ and increased expression of TNF- α and IFN-y mRNA.²⁰ Our findings strengthen the body of evidence that there is systemic immune and inflammatory activation in PPS-patients. This is clinically relevant because systemic inflammation has regularly been found in people with muscle wasting due to chronic disorders such as AIDS, chronic heart failure, COPD, and cancer cachexia and in normal ageing.²⁷⁻³⁰ The enhanced levels of TNF- α , IL-6, IL-8 and leptin in PPS-patients, as opposed to normal levels of IFN- γ , IL-1 α , IL-1 β , IL-1RA, IL-10, IL-13, IL-17A and IL-18 are indicative of the involvement of specific inflammatory pathways and exclusion of other pathways.

 $TNF-\alpha$ is a key pro-inflammatory mediator which is produced systemically predominantly by monocytes, and stimulates the release of pro-inflammatory cytokines and prostaglandin

inflammatory mediators from macrophages.³¹ The elevated levels of TNF- α in our PPSpatients and the strong correlations between TNF- α and IL-6/IL-8, both of which are induced by TNF- α , suggest that monocytic TNF- α drives systemic inflammation in PPS. A clinically relevant finding as TNF- α can potentially lead to skeletal muscle wasting through increased muscle protein breakdown, reduced skeletal muscle anabolism, and reduced IGF1 expression locally (while IGF1 protects against cell apoptosis).²⁹

Leptin levels were strongly related to BMI in our patients, which is not unexpected since this immune mediator is largely produced by adipose tissue.³² When dysregulated leptin can cause inflammatory responses, by upregulating monocytic production of IL-6, TNF- α and IL-10, such as happens in MS.³³ In this study however, leptin levels did not correlate with levels of any of the other mediators, suggesting leptin is not driving the systemic inflammation in PPS as it does in, for example, obesity.³² The lack of significantly raised levels of IFN- γ and IL-17A in PPS, which are produced mainly produced by specialised cells such as T-cells and innate lymphoid cells, excludes a major role for these cells in driving systemic inflammation in PPS. However, the raised IL-17A levels in a large subgroup of our patients and its correlation with levels of the other pro-inflammatory mediators (including TNF- α) are interesting. Elsewhere, IL-17A has been shown to synergize with TNF- α to exaggerate production of pro-inflammatory mediators, leading to tissue damage.^{34,35} Perhaps then, this plays a small role in the inflammatory response in PPS as well.

The lack of enhanced levels of IL-1 β and IL-18 excludes a role for inflamma some activation in PPS.

Differential expression of anti-inflammatory mediators could also potentially underlie chronic inflammation. In this study however, we found no significant differences between levels of anti-inflammatory mediators IL-10 and IL-1RA of patients and controls. Although IL-1RA was relatively enhanced in a large subgroup of patients, it is unlikely that this indicates a systemic anti-inflammatory response to raised levels of pro-inflammatory mediators IL-1a and β – which are counteracted by IL-1RA – as levels of these mediators were not enhanced. IL-1RA levels may just be a reflection of local activation.

We found no evidence for a direct relationship between elevated concentrations of immune mediators and change in clinical parameters. Neither when those with increased immune mediators were compared to those with normal levels (Table 4.4), nor when the group was regarded as a whole (example Figure 4.1). Only one other study investigated this

relationship systemically previously, using a limited panel of mediators. They reported no associations between serum leptin concentrations and cross-sectional clinical parameters and weak associations between raised serum $TNF-\alpha$ and (muscle) pain, and none with muscle strength.¹⁹ Thus, based on findings so far, there is little evidence for a relationship between the systemic inflammation seen in PPS and the symptoms related to muscle wasting. However, our findings also do not preclude a role for these mediators in PPS symptomology as the effective concentration locally (in the CNS and muscle fibres) may deviate from the systemic concentrations.²⁹ Also, skeletal muscle in PPS may show increased expression of proinflammatory mediators, allowing increased local catabolic action of these mediators, as has been found in other chronic disease states.²⁹ Although no studies have investigated mediator levels at a muscular level in PPS, several have found increased mRNA expression of various inflammatory mediators and increased levels of protein abnormalities in cerebral spinal fluid.13,14,20,36 Treatment with IVIG has moreover been shown to reduce mRNA expression in the central nervous system.¹³ The effects of IVIG treatment on clinical symptoms of PPS have been less clear. A comprehensive Cochrane review including a meta-analysis of available studies up to 2015 revealed inconsistent effects on muscle strength and no effect on activity limitations.⁴ So as yet, it is unclear whether the symptomology of PPS is related to systemic or CNS inflammation and whether it can be influenced by drugs that reduce levels of inflammatory mediators.

A particular strength of this study is that we investigated a wide range of pro-inflammatory and immune-modulatory mediators, which allowed a more comprehensive analysis of the pathways potentially involved in the immune response in PPS than published previously. Also, we included a measure of denervation in addition to the functional clinical parameters commonly used. Comparison of the levels of inflammatory mediators and the rate of clinical decline rather than the clinical situation at one moment, was another novel addition to the existing literature. In contrast to previous studies we assessed mediators in plasma rather than in serum. The advantage of plasma over serum is that blood cells are removed from plasma, so that active clotting and involvement of cells may not affect levels of inflammatory mediators, especially when the samples are prepared swiftly after venepuncture as in this study. The choice to investigate levels of circulating inflammatory mediators also has an advantage over studying mRNA expression in circulating cells as the latter need not correlate with the quantity of mediators actually produced and active.³⁷ A limitation in this study is that we investigated muscle strength and denervation in one muscle only. The quadriceps muscle studied here is a large and functionally important one, but including multiple muscles bilaterally would have better represented overall levels of (and decline in) strength and innervation. A second limitation is that we did not have inflammatory mediator measures at baseline. We believe the comparison between the one time immune mediator measurements and change in clinical parameters is nevertheless valid, based on the assumption that PPS involves a chronic rather than an acute inflammation in PPS. Additional investigations of local levels of inflammation in CNS or muscle tissue were not feasible in this study, but would be valuable topics for future research.

Conclusion

The elevated levels of inflammatory mediators in plasma confirm the presence of systemic inflammation in PPS and there are indications that monocytic TNF- α may drive these responses. However, we found no evidence for a relationship between this systemic inflammation and long-term declines in walking capacity, strength or motor unit size. Because local levels of inflammation may differ from systemic ones, the finding of systemic inflammation might still be clinically significant in PPS. Future research should focus on the relationship between local levels of inflammation of muscle tissue or CNS and clinical characteristics of the muscle.

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Section C

Physical mobility problems in polio survivors

Chapter 5

Change in physical mobility over 10 years in post-polio syndrome

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Abstract

Introduction: Post-polio syndrome is characterised by progressive muscle weakness and other symptoms which can limit physical mobility.

Methods: We assessed the rate of decline in mobility over 10 years in relation to strength decline; and investigated potential predictors for the rate of decline of walking capacity, a measure of mobility, in 48 patients with post-polio syndrome and proven quadriceps dysfunction at baseline.

Results: Average walking capacity and self-reported physical mobility declined over 10 years, by 6 and 14%, respectively. Concomitantly people lost an average of 15% of isometric quadriceps strength. Significantly more people used walking aids offering greater support at follow-up. Notably, there was much individual variation, with 18% of participants losing a substantial amount of walking capacity (27% decline) and concomitant self-reported physical mobility(38% decline). Loss of quadriceps strength only explained a small proportion of the variance of the decline in walking capacity (R = 11%) and the rate of decline could not be predicted from baseline values for strength, walking capacity, self-reported physical mobility or basic demographics.

Conclusion: The individual variability, yet lack of predictive factors, underscores the need for personally tailored care based on actual functional decline in patients with post-polio syndrome.

Introduction

Post-polio syndrome (PPS) is characterised by progressive loss of muscle strength and/or endurance after at least 15 years of stable neurological functioning.¹ It is often accompanied by symptoms of generalised fatigue, and muscle and joint pain.¹

The pathophysiology behind PPS is not fully understood, but a combination of distal degeneration of axons of enlarged motor units caused by increased metabolic demands² and the normal aging process, is the most widely accepted aetiology. Additionally inflammatory mechanisms are thought to be involved.^{3,4} The resulting strength decline, may negatively affect physical mobility and restrict participation in activities

of daily life.^{1,5-8} The rate with which physical mobility deteriorates in patients with PPS, and to what extent a continuing loss of muscle strength contributes to this decline, is however still an issue of debate.⁹

Longitudinal studies to date that included measures of physical mobility such as walking capacity and self-reported physical mobility reported conflicting results.¹⁰⁻¹⁶ Moreover, the direction of the change in physical mobility did not always match expectations based on concomitant strength changes.¹⁰⁻¹⁵ A possible explanation for the variable results found is that the follow-up period of some of these studies was shorter than the recommended 4 years.^{17,18} While the longer studies included polio survivors with and without PPS and a wide array of initial deficits and used a great variety of different outcome measures to measure physical mobility. Additionally, no study so far evaluated predictors for a decline in walking capacity in PPS, while knowledge thereof would allow for targeted and timely intervention to either prevent further decline of mobility or reduce the consequences of this decline. For these reasons, a long-term study in a homogenous cohort of patients with PPS is urgently needed.

In 2000, we assessed physical mobility and quadriceps strength in a group of 66 patients with PPS who had proven involvement of at least one quadriceps muscle.¹⁹ By studying this homogenous group of patients with defects in a functionally important muscle after 10 years, we aimed to assess the long-term rate of decline in physical mobility in relation to strength declines and to investigate potential predictors of the rate of deterioration of walking capacity in PPS.

Methods

Participants

Sixty-six adults with PPS that had completed baseline measurements in a randomized controlled trial of pyridostygmine between 1999 and 2001, were invited to participate in the present study (2010).¹⁹ At baseline, ambulatory individuals with PPS were included if they had (1) symptoms of fatigue; (2) symptoms of post-poliomyelitis muscle dysfunction in at least one quadriceps muscle; (3) neuromuscular transmission defects in the symptomatic quadriceps muscle; (4) a minimum quadriceps strength of 30 Nm; and (5) age between 18 and 70 years. Exclusion criteria were significant neurological, orthopaedic, cardiovascular pulmonary, or endocrine disorders, and anaemia or thyroid dysfunction.¹⁹

No new inclusion criteria were applied in the present follow-up. The only new exclusion criterion was the presence of any newly developed disease that affected voluntary control of the muscles. All participants provided written informed consent, and the study was approved by the institutions' Medical Ethics Committee.

Study design

In this prospective cohort study, all participants underwent a standardized assessment of functioning on two separate days, in most cases within two weeks and never more than 3 months apart (Figure 5.1). Data from high-density surface EMG measurements included on day 2 has been reported elsewhere.²⁰

Measurements

Basic demographics

Age, gender, number of years since acute poliomyelitis, and the number of extremities clinically affected by the disease were registered at baseline. The number of people with new symptoms of muscle weakness, muscle fatigue, muscle pain, and atrophy were recorded both at baseline and follow-up. In addition, people reported whether each symptom had increased, decreased, or remained stable at follow-up compared to baseline.



Figure 5.1 Inclusion figure and overview of measurements performed on each testing day.

Abbreviations: PPS = post-polio syndrome; HDsEMG = high-density surface electromyography. ^a Four patients were excluded for co-morbidities that may have affected the quadriceps under investigation: 1 was in hospital for treatment at the time of measurement, 1 had a prosthetic joint infection and loosening of a knee prosthesis and 2 were suffering from lower limb muscle sprains and strains after a fall. ^b For the subject unable to travel to the day 1 location, intake and questionnaires were completed on day 2, data from two minute walk test remained missing.

Physical mobility and strength

Walking capacity: The distance walked (m) in two minutes at a comfortable pace on a standardised 50 m circuit was recorded.²¹ Participants used the same assistive walking devices they used in daily life.

Self-reported physical mobility, Nottingham health profile (NHP): The Dutch validated NHP measures perceived health and consists of 38 polar questions in 6 subscales.²² The subscale physical mobility (NHP-PM) consists of 8 items and the sum score ranges from 0 (good physical mobility) to 100 (poor physical mobility).

Assistive walking devices: The type of walking aid and lower limb support device (i.e. orthosis or orthopaedic shoes) used when walking outside was categorised according to severity (Table 5.2).

Quadriceps strength: Peak knee extension strength (Nm) was defined as the strongest of three isometric maximal voluntary contractions performed on a hard surfaced fixed chair

dynamometer with knee and hip flexed at 90 deg. At baseline, strength measurements were performed on the strongest symptomatic quadriceps muscle of each participant, and the same leg was tested at follow-up. In healthy controls, the strongest leg was chosen unless unilateral joint or muscle problems were present.

Statistical analysis

Statistical analysis was performed with the SPSS statistical software package (version 19.0.0.1). Means with standard deviations (SD), medians with interguartile range (IQR), and percentages were used to describe the population. Paired samples t-tests were used to test the significance of change in continuous variables. The assistive walking devices used were categorised according to severity and changes over time tested with Wilcoxon signed rank test. Associations between the changes in the physical mobility outcomes and muscle strength were investigated using Pearson's correlation coefficient. To identify potential prognostic factors for change in walking capacity, associations with baseline parameters were first investigated with Pearson's correlation coefficient. In case of multiple significant univariate associations (p < 0.10) these factors were then entered into a forward stepwise linear regression model. Because of great individual variability in the change in walking capacity, an extra subgroup analysis was added retrospectively. A decline of >23 meters on the walking test (i.e. beyond the 95% confidence limits of measurement error²¹) was considered a substantial decline. We compared the subgroup of patients with a substantial decline in walking capacity with the remaining patients with a smaller decline or improvement in walking capacity. Within these subgroups changes over time were analysed with paired samples t-tests and between subgroup differences with independent t-tests. Significance for all analyses was set at p < 0.05.

Results

Participants

Forty-nine patients (74%) with PPS were included in the analysis. Non-participants were untraceable (n=6), deceased (n=2), unwilling (n=4), or excluded for co-morbidities that may have affected the quadriceps under investigation (n=4) (Figure 5.1). One patient with PPS was unable to adhere to the measurement protocol and was excluded from all analyses. Demographics, disease and mobility-related characteristics of participants did not differ

from non-participants (Table 5.1). At baseline 48 participants (98%) had complaints of muscle weakness, 45 (92%) of muscle fatigue, 35 (71%) of muscle pain and 22 (45%) of muscle atrophy. At follow-up most reported that these symptoms had worsened over time: 80% experienced more muscle weakness, 80% more muscle fatigue, 63% more muscle pain, and 45% more atrophy, compared to baseline.

Parameter	Participants (n=49)	Non-participants (n=17)
Age (years)	52±8	51±6
Age acute polio (years)	2 [1–4]	1 [0.5–3.5]
Time since polio (years)	49±9	49±6
Sex, female (count)	31 (63)	11 (65)
Number of clinically affected limbs (count)	1 [1–2]	1 [1–1]
Walking capacity (m)	120.3±24.8	118.3±21.6
NHP-PM [0–100]	35±18	37±23
Quadriceps strength (Nm)	64.4±33.8	61.8±35.3

Table 5.1 Baseline characteristics participants and non-participants

Abbreviations: NHP-PM = physical mobility subscale of the Nottingham health profile; Values are means \pm standard deviation, medians [IQR] or number of subjects (%).

Change in physical mobility and strength

Walking capacity and self-reported physical mobility declined significantly over 10 years by 6% and 14%, respectively (Table 5.2). At follow-up, significantly more people used walking aids than at baseline and there was shift towards types of assistive devices that offer increased support (Table 5.2). None of the patients lost ability to ambulate. Patients who became wheelchair-dependent for outdoor transportation (n=2) were able to walk inside the house (Table 5.2).There was no significant change in the number of people using lower limb supportive devices or the type of device used (Table 5.2). Quadriceps strength declined significantly by 15% over 10 years (Table 5.2).

Predictors of change in walking capacity

Change in walking capacity was significantly correlated to change in quadriceps strength (r=0.333, p=0.024) and change in self-reported physical mobility (r=-0.425, p=0.003). Baseline age, gender, time since acute polio, quadriceps strength, walking capacity and self-reported physical mobility, were not associated with the change in walking capacity
(Table 5.3). A multivariable prognostic model could therefore not be built. There were large individual differences in change in walking capacity, and 9 participants (18%) had a decline above the measurement error (larger than 23 m) over 10 years (128±30 m to 94±24 m, or 27% decline, p<0.001). Baseline clinical characteristics of these patients were not significantly different from those of patients without a substantial decline, except for gender (67% was male as supposed to 31% in the group without substantial declines). Subgroup analysis revealed that these participants had a concomitant large, not significant, decline

	T _o (n=49) mean±SD or n (%)	T ₁ (n=49) mean±SD or n (%)	Change mean±SD	<i>p</i> -value
Physical mobility				
Walking capacity (m) ^{a, c}	120.3±24.8	113.6±31.3	-6.7±20	0.024*
NHP-PM [0–100] ^c	35±18	40±19	5±12	0.004**
Walking aid outside ^d				
Wheelchair	0	2 (4)	NA	< 0.001**
Rollator	1 (2)	6 (12)		
2 canes or crutches	6 (12)	9 (18)		
Cane or crutch	15 (31)	15 (31)		
None	27 (55)	17 (35)		
Lower limb support, outside ^d				
KAFO	3 (6)	6 (13)	NA	0.244
AFO	6 (12)	4 (8)		
Orthopaedic shoes ^b	14 (29)	15 (31)		
None	26 (53)	24 (49)		
Strength (Nm) ^{a, c}	64.4±33.8	54.7±32.6	-9.6±20.9	0.003**

 Table 5.2
 Change in physical mobility and strength over 10 years

Abbreviations: T0 = baseline; T1 = follow-up; NHP-PM = Nottingham health profile questionnaire, physical mobility category; AFO = Ankle-foot orthosis; KAFO = Knee- ankle-foot orthosis; NA = not applicable. ^a One subject is missing from walking capacity (n=48) and 2 subjects are missing from strength (n=47) measurements. ^b Orthopaedic shoes were only scored if no AFO or KAFO was present. ^c Paired Student's t-test. ^d Wilcoxen signed rank test. Significant at ^{*} p<0.05 and ^{**} p<0.01.

Baseline characteristics	Correlation with change in walking capacity $(r)^a$	<i>p</i> -value
Walking capacity	-0.036	0.808
NHP-PM	-0.036	0.809
Quadriceps strength	0.091	0.539
Age	-0.116	0.431
Gender	-0.022	0.884
Time since polio	-0.108	0.467

Table 5.3 Associations between baseline parameters and change in walking capacity

^a Pearson's correlation coefficient, r.

in self-reported physical mobility (29 ± 14 to 40 ± 16 , or 38% decline, p=0.052) and muscle strength (72 ± 41 Nm to 52 ± 42 Nm, or 28% decline, p=0.071). The mean decline in strength did not differ significantly between this subgroup and the remaining participants (Figure 5.2).



Figure 5.2 Change in quadriceps strength for those with and without a decline in walking capacity larger than the smallest detectable difference (>23m).

Discussion

After 10 years, observed and self-reported physical mobility declined in patients with PPS and symptomatic quadriceps involvement and more people used walking aids offering increased support. People also reported a continued increase in symptoms of muscular weakness,

fatigue, pain and atrophy. The rate of change in walking capacity was weakly related to rate of change in quadriceps strength, but could not be predicted from any baseline parameter including walking capacity, self-reported physical mobility or quadriceps strength. Although overall loss of walking capacity was modest, there was a great degree of individual variability and approximately one fifth of the group experienced substantial declines. This subgroup with the largest declines also experienced a large loss of self-reported physical mobility.

Although we studied a homogenous group of patients with PPS, all with proven quadriceps dysfunction, the decline in walking capacity and self-reported physical mobility was comparable to rates previously reported.¹⁰⁻¹⁶ The rate of decline in walking capacity (0.6% annually) fell within the range of that reported in three of the four previous longitudinal studies among polio survivors (i.e. 0.2-2%).¹²⁻¹⁴ Two of these studies^{12,13} included patients with late onset symptoms, not necessarily meeting the diagnostic criteria for PPS. The remaining study reported no change in walking capacity,¹⁰ but had a limited follow-up time (1.4 years) and used the 10m walk test, which has less favourable clinimetric properties compared to longer walking tests.²¹ The comparable rate of decline in walking capacity and self-reported physical mobility in this diagnostically homogenous group of PPS patients is surprising and suggests that on average the rate of decline in patients with PPS does not differ from that in other patients with polio sequelae. The decline in walking performance in daily life may have been greater than the decline in capacity assessed under test conditions, since walking in daily life is more demanding than walking under optimal conditions.²³ Comparison of the rate of decline in self-reported physical mobility with previous studies is impeded by the use of a great variety of questionnaires, which each measured different aspects of physical ability or handicaps.^{10,11,13-16} The one study that also used the unweighted NHP-PM found a significant improvement in self-reported physical mobility in the first year followed by a steady decline over the following 5 years, at a similar rate (1.5% per year) to that found in our study (1.4% per year).¹¹

While overall the average rate of decline of physical mobility found in this study was modest we noted a large individual variability, with almost a fifth of the group experiencing a substantial decline in walking capacity. This individual variability, similar to that found in a previous study,¹⁴ emphasizes the importance of identification of predictors for loss of walking capacity, as this would allow targeted patient selection for suitable intervention strategies. The main focus in our analysis was quadriceps strength because reduced strength in this large lower limb muscle has previously been associated with reduced walking capacity,^{24,25} reduced postural control,^{7,26} and a higher risk of falls^{7,26,27} in cross-sectional studies among

polio survivors. In this longitudinal study, initial quadriceps strength was not a predictor of the rate of decline in walking capacity and the rate of strength decline only explained a limited proportion of the variability in decline in walking capacity (r=0.333, i.e. 11% explained variance). Moreover, those with substantial declines in walking capacity appeared to experience a similar loss of strength to the remainder of the group (Figure 5.2), although the limited number of participants with substantial declines means these conclusions are tentative. A possible explanation for the small contribution of strength change to change in walking capacity in this study is the fact that only one quadriceps muscle was measured. Changes in other muscles in the same and contralateral leg, as well as compensatory strategies such as hyperextension of the knee and use of assistive walking devices, might allow a person to maintain walking capacity despite loss of quadriceps strength.^{24,25,28} It was not possible to incorporate these factors in the analysis here as it is not known to what extent these factors affect the speed of walking. Furthermore, a loss of strength might only affect walking capacity after dropping below a certain, as yet undetermined, functional threshold.^{25,29,30}

The lack of prognostic factors and limited explanatory capacity of quadriceps strength for the decline in walking capacity indicates that it was not possible to identify patients with high risk of deterioration despite the fact that we investigated a homogenous cohort with respect to quadriceps affectation. The clinical implication is that the decision of which patients to monitor closely should be decided on actual findings of ongoing functional decline, rather than on one time measurements of neuromuscular dysfunction. Potentially useful interventions will moreover need to be provided in highly personalised care programmes.

This study had some potential limitations. Exclusion of people with co-morbidities directly affecting voluntary control of the leg muscles at follow-up and patient-initiated drop-out could theoretically result in the loss of patients with more severe disease progression. However, the exclusion criteria ensured that the measured changes in physical mobility in this group could be ascribed to PPS rather than to co-morbidities and, at least at baseline, non-participants were not more affected than participants.

Another important methodological limitation is the fact that muscle strength measurements were performed in only one quadriceps muscle. In studying prognostic factors for decline in walking capacity and physical mobility it would have been better to analyse muscle strength of both quadriceps muscle groups and even other leg muscles. It must however be realised that the chosen side for the strength measurement was the quadriceps with symptoms of post-poliomyelitis muscle dysfunction.

For our subgroup analyses, we might have underestimated the number of people with a substantial loss of walking capacity because the measurement error (i.e. 0.19 m/s (or 23 m)) previously determined in polio survivors was high.²¹ The clinically relevant threshold may be lower, since a 0.1 m/s slower gait speed (or 12 m) is associated with a 12% higher mortality in older adults without polio.³¹

The NHP-PM may lack responsiveness to detect changes in self-reported mobility as it has been found to be a little sensitive measure in other patient groups.³² Therefore, we may have underestimated the loss of perceived mobility as more subtle changes might not be registered using this instrument.

A particular strength of this study was the inclusion of a homogenous group of patients with PPS with symptomatic quadriceps muscles. The knee extensors are key muscles for walking. Therefore, studying this selected group allowed observation of changes in mobility problems in a severely affected group, which has not been reported before. Also, the long follow-up period was valuable as there are only few long-term studies on functional changes,^{11-14,16} while a minimum of 4 years is recommended due to the large within subject variability for functional measurements.^{17,18}

Conclusion

This long-term study in a homogenous group demonstrated that on average, physical mobility of patients with PPS and symptomatic quadriceps muscles declines at a modest rate. However, approximately one fifth of the group had substantial declines in walking capacity, emphasising the importance of attention to this problem in certain individuals. Which individuals were to decline substantially, could not be predicted by baseline quadriceps strength or walking capacity and the substantial declines were not always accompanied by large quadriceps strength declines. These findings underscore the need for personally tailored care, which is primarily symptomatic or supportive; and should be based on actual functional decline, rather than on one time strength or walking capacity measurements.

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Chapter 6

Circumstances and consequences of falls in polio survivors

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Abstract

Objectives: Many polio survivors suffer from symptoms that are known risk factors for falls in the elderly. This study aims to determine (1) the frequency (2) consequences (3) circumstances and (4) factors associated with falls in polio survivors.

Methods: A survey was conducted among 376 polio survivors. Participants completed a falls history questionnaire and additional information was obtained from the medical files.

Results: Of the 305 respondents, 74% reported at least one fall in the past year and 60% two or more. 16% of fallers described a major injury after a fall in the last year and 69% reported fear of falling. A third of fallers had reduced the amount they walked because of their fear of falling. Most reported falls in a familiar environment (86%), during ambulation (72%) and in the afternoon (50%). Quadriceps weakness of the weakest leg (MRC≤3), fear of falling and complaints of problems maintaining balance were independently associated with both falls and recurrent falls, while increasing age and medication use were not.

Conclusion: The high rate of falls and consequences thereof, merit the implementation of fall intervention strategies. To maximise effect, they should be tailor-made and target the falls mechanisms specific to polio survivors.

Introduction

Falls are a clinically important, but underrated problem for poliomyelitis survivors. Curiously, there has been little research on the topic, while an estimated 10 to 20 million people worldwide¹ and 15,000 in the Netherlands² are now living with the consequences of polio. Many polio survivors suffer from a variety of symptoms that are known risk factors for falls in the elderly and patients with neuromuscular diseases (NMD).³⁻⁹ In particular, they often have extensive muscle weakness that exists either as a remnant of the primary infection or appears and progresses later in life as a part of post-polio syndrome (PPS).¹⁰⁻¹² In addition, other late symptoms such as muscle & joint pain, cold intolerance and fatigue, may contribute to the occurrence of falls.¹⁰

Studies of fall frequency among polio survivors to date have confirmed the clinical observation that falling is a problem in this group, with 50 to 84% of participants reporting at least one fall each year.^{5,11-14} This yearly fall incidence is considerably higher than that in elderly people, where it is 17–23% for people over-55 years of age^{15,16} and 32–42% for those over 75 years of age.^{17,18} Figures pertaining to consequences of falls in polio survivors are equally alarming. One study found that 96% of an outpatient population had osteopenia or osteoporosis and reported a fracture incidence of 38% over 5 years.¹⁴ Another study reported, that 61% of 233 community based participants had required medical attention at some point as a result of a past fall and 35% had suffered a fracture.¹³ In addition, more than three-quarters described a fear of falling (77%) and many changed their lifestyle because of this fear (62%).¹³ Another study reported an even higher frequency of fear of falling, i.e. 95%.¹²

Among elderly people, targeted fall prevention programmes have successfully been implemented to reduce the number of falls in the population.^{3,17} Whether these interventions are also effective in polio survivors depends on whether the circumstances of falls and associated factors are comparable. Muscle weakness, increasing age, female sex, living alone, increasing disease severity, use of high risk drugs or polypharmacy and fear of falling are some of the numerous risk factors for falls in the elderly^{3,6,16,18-24} and people with neuromuscular diseases^{4,8} that might potentially be associated with falls in polio survivors as well. So far, only the first and last have been expressly studied in relation to falls in polio survivors,^{5,12} while circumstances of falls have only been explored in a pilot study.¹¹

The aim of the current study was to determine 1) the magnitude and severity of the problem of falling and 2) the circumstances of falls and associated factors among a large cohort of

polio survivors in the Netherlands in a retrospective cross-sectional study. The questions we aim to answer are:

- 1. How frequently do polio survivors fall?
- 2. What are the physical and psychological consequences of falls in polio survivors?
- 3. Under what circumstances do polio survivors fall?
- 4. Are patient characteristics that are known risk factors for falls in the elderly present and associated with falls in polio survivors?

Methods

Participants

Three hundred and eighty seven patients with a history of paralytic poliomyelitis visited the department of rehabilitation of the AMC between April 2003 and August 2009. Of these, eleven had to be excluded because they: had died (n=3), were younger than 18 years of age (n=3) or currently resided outside the Netherlands (n=5). The 376 patients who remained were asked to participate in the study. The hospital Medical Ethics Committee waived the need for ethical approval.

Falls history and disability questionnaire

Participants were asked to complete a questionnaire detailing their: current medical and physical condition, home environment, mobility, average fall frequency, the number of falls in the past year, injuries sustained as a consequence of these, fear of falling, reduction of activities because of this fear and the circumstances of the most recent fall. The questionnaire was based on that used in a previous study among community dwelling elderly¹⁵ and also incorporated the Dutch 10 item Falls Efficacy Scale (FES-10). Derived from the original by Tinetti et al.,²⁵ this FES has previously been used as a measure of fear of falling in the elderly²⁴ and is advised for Parkinson patients.²⁶ It allows people to denote how concerned they are about falling during each of ten activities on a 4 point scale, ranging from '0: not at all concerned' to '3: very concerned'. The maximum total score was 30. If a subject left one or two items unanswered the total score was divided by the number of answered items

and multiplied by ten. For a subject who left more than two items unanswered a sum score was not made, following the advice of the ProFaNE group.²⁷ Missing or unclear answers in the questionnaires were amended by telephone interviews where possible and analysed as missing if not.

Disease characteristics

Information concerning the extent of paresis, types and number of medications used and the history of poliomyelitis was extracted from the medical file of each participant. The strength of ankle dorsal- and plantar-flexion; knee extension and flexion; and hip extension, flexion, ab- and adduction are routinely assessed during outpatient visits using manual muscle testing (MMT) and scored according to the Medical Research Council scale (MRC).²⁸ For this study, the sum of the most recent MRC-scores of all aforementioned lower extremity muscle groups was calculated for each participant and used as a measure of extent of paresis.²⁹ If a patient had an arthrodesis, the muscle groups crossing that joint were scored as 0. The maximum possible score was 80 and incomplete sum scores were excluded from analysis. Information about the use of prescription medication taken from the questionnaires was supplemented with that extracted from the patient files where necessary. This allowed calculation of the number of drugs used by each subject and the frequency of use of certain classes of drugs that are potential risk factors for falls. Specifically, the use of sedatives and hypnotics (incl. benzodiazepines), antidepressants, antipsychotics and neuroleptics, anti-arrhythmetics, anticonvulsants, diuretics, digoxine and non-steroidal anti-inflammatory drugs (NSAIDs) was reviewed.¹⁸⁻²⁰ When subjects did not report actual names of drugs or classes of drugs they used and information from medical files was insufficient, the data was considered missing. Multiple drug use was defined as the use of four or more prescription drugs.²¹ The history of poliomyelitis that was sought consisted of: age at the time of infection, the country in which the primary infection was contracted and initially treated, and whether or not the definitive diagnosis post-polio syndrome (PPS) had been made.

Data analysis

The main outcome measures were self-reported frequency of falls, injuries sustained during a fall, fear of falling, FES-scores and the circumstances of falls. Circumstances of falls were described in terms of location, time of day, activity, ground surface, footwear and distractions during the most recent fall. A faller was defined as someone who had fallen at least once and a recurrent faller as someone who had fallen at least twice in the last year. Frequencies, means, standard deviations and proportions were used to describe the population and the main outcome measures. Differences in the prevalence of factors associated with falls between (recurrent) fallers and non-(recurrent) fallers and participants and non-participants were investigated using the Student t-test for continuous variables and the Chi-square test and Fisher Exact test for (dichotomous) nominal and ordinal variables. A logistic regression analysis was performed in order to create a model for the fall and recurrent fall risks of 'walkers' using the following 4 steps. 1) The full-time wheelchair users were removed from the analysis. 2) Relevant continuous variables were dichotomised using the median of each as a cut-off point. 3) Odds ratios (OR) were calculated for each dichotomous variable that was associated with falls or recurrent falls in the previous analysis (at p < 0.10). 4) The independent contribution of each variable with a significant OR in univariate analysis, was investigated in forward stepwise binary logistic regression analysis, providing an OR and 95% CI corrected for multiple testing. Significance was set at p < 0.05.

Results

Population

Three hundred and five of the three hundred and seventy six polio survivors who were approached returned their completed questionnaires (response rate 81%). Non-participants were significantly younger than participants and significantly more first generation immigrants did not participate, while differences in gender were not significant. Various other disease and mobility-related characteristics of participants are summarised in Table 6.1.

Frequency of falls

73.8% of patients (n=225) reported at least one fall in the last year (i.e. are **fallers**) and 60.3% (= 81.7% of fallers, n=184) at least two falls (i.e. are **recurrent fallers**) (Figure 6.1). Reported average fall frequency was similar, with 75.4 % (n=230) admitting to fall at least once yearly, 25.9% (n=42) monthly, 12.1% (n=31) weekly and 2% (n=6) daily.

Characteristics ^a	Participants (n=305)	Non-participants (n=71)
Age, mean years ± SD (range)	57.4 ± 11.4 (18–85)	47.1 ± 12.2 (21–88)**
Female, % (number)	63.6 (194)	52.1 (37)
Acute infection + initial treatment outside EU, % (number)	13.4 (41)	59.2 (42)**
Age at time of acute polio (n=298), mean years \pm SD (range)	3.7 ± 3.8 (0.04–26)	-
Duration since acute polio (n=298), mean years \pm SD (range)	54.6 ± 10.8 (17-82)	-
Definite diagnosis PPS, % (number)	70.5 (215)	-
Sum score MMT lower limbs (n=267), mean \pm SD	59.8 ± 17.7	-
Living alone, % (number)	30.5 (93)	-
Walking ability (n=303), % (number) Never walk Only walk indoors + around the house Walk outside, short + long distance	5.2 (16) 25.6 (78) 68.5 (209)	-
Type of walking aid in-/outdoors (n=289), % (number) ^c None Manual aid in-/outdoors ^b Wheelchair in-/outdoors	46.0 (133) 23.2/48.1 (67/139) 5.5/5.5 (16/16)	-
Orthopaedic shoes (n=289), % (number) ^c	51.9 (150)	-
Orthoses (n=289), % (number) ^c	42.6 (123)	-
Frequent physical complaints, % (number) Pain in joints or muscles Tiredness Reduced exercise tolerance Rigidity joints or muscles Back pain Problems maintaining balance Swollen feet Reduced sensation legs Respiratory problems/shortness of breath Palpitations	83 (253) 80 (242) 74 (226) 71 (217) 63 (193) 57 (173) 32 (98) 27 (83) 24 (73) 16 (50)	-

Table 6.1 Characteristics of participants and non-participants

Abbreviations: SD = standard deviation; PPS = post-polio syndrome: only includes those for whom the diagnosis is certain; MMT = manual muscle testing. ** p<0.01.

^a The number of participants for whom the information was available is noted behind each characteristic if it deviated from the total number of participants (i.e. 305); percentages were all calculated as a fraction of the real total (i.e. 305, exception see: ^c).

^b Manual walking aid: one/two cane(s), one/two crutch(es) or a walker.

^c Those 16 who "never walk" excluded from total in the percentage calculation for this item (i.e. total n=289).

Consequences of falls: injuries and fear of falling

Eighty percent of the fallers (n=180) had sustained at least one injury as a result of a fall in the past year. The majority (64%, n=144) suffered only minor injuries such as bruises, superficial cuts, scrapes and sprains or strains. However, 15.6% of fallers (n=35) described



Figure 6.1 Frequency of falls in the last year (n=305).

additional major injuries. 7.1% had a fracture (n=16), just under half of whom required hospital admission; 3.1% (n=7) required hospital admissions for injuries other than a fracture (14 admissions in total=6.2%) and 5.3% (n=12) had one or multiple other serious injuries not requiring hospital admission. The latter category included: 5 head injuries (concussions, loss of consciousness, broken teeth,) 3 dislocations (shoulder, knee) and a variety of 5 other thigh, knee and foot injuries with severe repercussions. Three people reported memory loss after the most recent fall without head trauma or loss of consciousness. As the extent of the loss was unknown they weren't included in the category 'serious injuries'.

Sixty three percent of responders answered positively to the question 'are you afraid of falling' (n=193) and 22.6% (n=69) had reduced their walking activity due to this fear. The mean total FES-score was 7.1 (SD 6.7) among the 285 people who completed the scale. There was a significant difference in fear of falling, FES-scores and reduction of activities between (recurrent) fallers and non-(recurrent) fallers (see Table 6.2). Four items of the FES were particularly worrying activities to many participants, i.e. 'showering or bathing' (72% had a FES-score of ≥ 1), 'de- or ascending stairs' (65.2%), 'walking around the neighbourhood' (51.5%) and 'food shopping' (48.2%). People were also more often 'fairly' and 'very concerned' during these activities than during the other six.

	Faller (n=225/212ª)	Non-faller (n=80/76)	<i>p</i> -value	Recurrent faller (n=184/174)	Non-recurrent faller (n=121/114)	<i>p</i> -value
Fear of falling, % (n)	69.3 (156)	46.2 (37)	<0.001**	70.7 (130)	52.1 (63)	0.001**
Mean FES, \pm SD (288 ^b)	8.0 ± 6.3	4.7 ± 5.4	<0.001**	8.6 ± 6.5	4.9 ± 5.1	<0.001**
Total FES ≥10, (%) (288 ^b)	34.0	14.5	0.0018**	39.7	12.3	<0.001**
FES ≥1, (%) ^c						
Cleaning the house (284)	44.5	26.7	0.007***	49.1	25.2	<0.001**
Getting (un-)dressed (291)	36.7	22.4	0.022*	39.3	23.0	0.004
Preparing simple meals(287)	24.1	8.0	0.003**	25.7	10.7	0.002
Taking a bath/shower (297)	76.7	66.7	0.082	77.8	68.4	0.071
Going to the shop (292)	57.2	31.2	<0.001	59.0	36.8	<0.001
Getting in/out of a chair (292)	34.0	15.6	0.002**	36.4	18.1	0.001
Going up/down stairs (279)	76.8	55.6	0.001"	77.6	61.5	0.004
Walk around neighbourhood (284)	62.4	35.1	<0.001	65.3	39.6	<0.001
Reaching down into cupboard (288)	46.2	36.8	0.157	50.6	33.3	0.004
Answering telephone (290)	37.4	21.1	.000	39.2	23.7	0.006"
Walk less due to fear of falling, %(n)	27.2 (61)	10 (8)	0.003**	29	13.2	0.002
Abbreviations: FES = falls efficacy scale; SD = st ^a The first number is the total number of fallers.	tandard deviation. All,	<i>p</i> -values are unc number of faller	orrected. s who completed t	he FES.		

Table 6.2 Fear of falling and consequential decreased walking activity relative to fall status

^b Seventeen people did not fill in FES completely and were excluded from analyses involving total FES-score. ^c The total number of people who scored a FES-item is noted between parentheses behind each item.

Significant at * p < 0.05 and * p < 0.01.

Circumstances of falls

The circumstances of participants' most recent fall are detailed in Table 6.3. The majority of falls occurred in a familiar environment, more than half in or around the home. Four fifths of all indoor falls occurred inside the home, while four fifths of all outdoor falls occurred away from the home. With one exception, all falls occurred during daytime, approximately half of these in the afternoon. Almost three quarters of the group fell while walking, de- and ascending stairs or during posture changes or transfers. 72.4% (21/29) of those in the latter category fell while attempting to get up from a seated position. In one third of the cases the

Circumstance (n) ^a		Frequency, % (n) ^b
Location, familiar (220)		86.2 (194)	
Location, subdivided (216)			
Inside Home Away from home ^c Familiar Unfamiliar	Outside Home Away from home ^c Familiar Unfamiliar	49.8 (112) 39.6 (89) 10.2 (23) 6.7 (15) 3.6 (8)	46.2 (104) 10.2 (23) 36 (81) 28 (63) 8 (18)
Time of fall (198) Morning Afternoon Evening Night		22.7 (51) 44.9 (101) 20 (45) 0.4 (1)	
Activity prior to falling (212) Walking Transfer/change of posture De-/ascending stairs Various tasks in & around house ^d		54.7 (123) 12.9 (29) 4 (9) 22.7 (51)	
Type of ground underfoot (217) Uneven surface Slippery surface Other		20.9 (47) 11.1 (25) 63.6 (143)	
Shoes worn at time of fall (212°) Normal Orthopaedic Open backed shoes/slippers None		54.8 (119) 23.5 (51) 9.7 (21) 9.7 (21)	
Need help to get up after fall (222)		33.8 (76)	

^a The total number of fallers (max 225) who reported the circumstance is noted after each item.

^b Percentages were calculated as a fraction of total number of fallers (i.e. 225, exception see ^e).

^c Including among others: 'on the street', 'in the snow', 'at a swimming pool', 'in a shop', 'at work' and 'at the sports club'.

^d These included more complex tasks such as 'doing the washing', 'gardening' and 'cleaning'.

^e The 8 full-time wheelchair users who are fallers were excluded from footwear analysis (i.e. total n=217).

ground underfoot was noted as being either uneven or slippery. Over half the fallers were wearing normal shoes when they fell and interestingly, only 44% of the fallers who had orthopaedic shoes were wearing them at the time of the fall (51/116.) One third of people could not rise after a fall without aid. 16.4% was distracted by an environmental factor just before the fall. Five people reported to have lost consciousness *before* the fall.

Factors associated with falls

The associations between fall status and factors potentially associated with falls can be seen in Table 6.2 and 6.4. Both falls and recurrent falls were associated with significantly more weakness of knee extensors of the weakest leg; complaints of maintaining balance and reduced sensation in the legs; fear of falling (both in the answer to the question 'are you afraid of falling', the total FES and 8 individual items of the FES, Table 6.2); and reduced ambulation due to this fear. In addition, single falls were also associated with more weakness of the lower limb in general (sum score); orthoses use and complaints of rigidity of joints and muscles, while recurrent falls were also associated with younger age and an extra item of the FES.

Other patient characteristics such as the diagnosis PPS, living alone and walking ability were not significantly associated with single or recurrent falls (Table 6.4). Also, no form of prescription medication use was associated with fall frequency (not single or multiple drug use or the use of specific drug classes, Table 6.4). It should be noted however, that the limited use of some of the evaluated 'high risk' prescription drugs made the groups too small for reliable statistical comparison.

The odds ratios for those variables significantly associated with falls or recurrent falls (n.b. walkers only, n=289) are shown Table 6.5.

Stepwise binary logistic regression analysis revealed that fear of falling, an MRC-score of less than 3 for the knee extensors of the weakest leg and complaints of problems maintaining balance were independently associated with both falls and recurrent falls. Non-independently associated variables were removed from the regression model in order to reduce the number of missings (i.e. sum MRC: 31 missing, FES: 16 missing) and allow more accurate calculation of odds ratios (Table 6.6).

Table 6.4 Factors potentially associated v	vith falls, stratifie	d by fall status				
Potentially associated factors	Faller (n=225)	Non-faller (n=80)	<i>p</i> -value	Recurrent faller (n=184)	Non-recurrent faller (n=121)	<i>p</i> -value
Age, mean years ±SD	57.1±11.8	58.5±9.9	0.316	56.3±12.2	59.2±9.7	0.022*
Female, %	62.7	66.2	0.567	60.3	68.6	0.142
Acute infection & treatment outside EU, $\%$	15.1	8.8	0.152	16.3	9.1	0.071
Definite diagnosis PPS, %	71.7	68.8	0.612	70.3	71.9	0.768
MMT lower limbs, mean ±SD ^a						
Sum score (267)	59.6±15.8	65.8±16.2	0.007**	59.6±15.9	63.5±16.2	0.056
Hip flexion weakest leg (283)	3.2±1.7	3.5±1.8	0.157	3.2±1.7	3.4±1.7	0.307
Knee extension weakest leg (281)	2.7±1.9	3.2±2.0	0.031*	2.6±1.9	3.1±1.9	0.041*
Ankle dorsal flexion weakest leg (282)	2.0±1.9	2.5±2.1	0.120	2.0±2.0	2.4±2.1	0.133
Living alone, %	32.4	25.0	0.214	32.6	27.3	0.322
Walking ability %						
Never walk	3.6	10.1	0.081	3.8	7.5	0.358
Only walk indoors+around the house	26.3	24.1		26.8	24.2	=
Walk outside, short + long distance	70.1	65.8	Ш	69.4	68.3	II
Walking aid, %						
Manual aid ^b in-/outdoors ^a Wheelchair in-/outdoors	24.4/51.7 3.6/8.0	19.4/48.5 10.0/17.5	0.39/0.65	24.3/50.6 3.8/8.7	21.4/51.4 7.4/13.2	0.57/0.89
Orthopaedic shoes, $\%^a$	53.4	47.2	0.359	54.8	47.3	0.215
Orthosis, % ^a	47.0	29.2	0.008**	46.9	35.7	0.061

Chapter 6

Frequent physical complaints, %						
Pain in joints or muscles	83.1	82.5	0.901	83.7	81.8	0.670
Tiredness	81.3	73.8	0.150	82.1	75.2	0.148
Reduced exercise tolerance	73.3	76.2	0.609	73.4	75.2	0.720
Rigidity joints or muscles	74.2	62.5	0.047*	73.4	67.8	0.291
Back pain	66.2	55	0.074	67.4	57.0	0.066
Problems maintaining balance	64.4	35	<0.001**	67.4	40.5	<0.001**
Swollen feet	33.3	28.7	0.451	33.2	30.6	0.638
Reduced sensation legs	30.7	17.5	0.023*	31.5	20.7	0.037*
Respiratory problems	23.1	26.2	0.572	21.7	27.3	0.268
Palpitations	14.7	21.2	0.172	14.7	19.0	0.317
≥1 medication, % (n) (280 ^c)	56.0 (116)	52.1 (38) 19.2	0.556	55.7 (93)	54.0 (61)	0.778
≥4 medications, % (n) (280 ^c)	14.5 (30)	(14)	0.344	13.8 (23)	18.6 (21)	0.278
Types of medications, $\%$ (n ^c)						
Benzodiazepines/hypnotics	5.3 (11)	9.6 (7)	0.200	6 (10)	7.1 (8)	0.715
Antidepressants	4.8 (10)	5.5 (4)	0.519	5.4 (9)	4.4 (5)	0.716
Anti-arrhythmics (all classes)	1 (2)	2.7 (2)	0.279 ^d	0.6 (1)	2.7(3)	0.182 ^d
Digoxine	1 (2)	0 (0)	0.546 ^d	0.6 (1)	(1) (1)	0.645 ^d
NSAIDs	19.3 (40)	23.3 (17)	0.470	19.8 (33)	21.3 (24)	0.763
Diuretics	11.1 (23)	8.2 (6)	0.486	10.2 (17)	10.6 (12)	0.906
Abbreviations: SD = standard deviation; PP ^a Sixteen full time wheelchair users remo users removed from 'walking aid outdoor ^b ie. carne(s), crutch(es) or walker ^c for 25 po	'S = post-polio synd ved from 'walking a rs' category. eople accurate infoi	rome; MMT=manual I aid indoors', 'orthopa rmation on which an	muscle testing, edic shoes; 'ort d how many pr	NSAID=non-steroida hosis' and 'MMT low escription drugs the	il anti-inflammatory drug. All p-v. er limbs' categories; 32 full time v used was not available, these c	alues are uncorrected. e outdoor wheelchair oeople were excluded

from this analysis (i.e. total n=280), $^{\rm d}$ Calculated with Fisher's exact test.

Significant at p<0.05 and p<0.01.

	Falls (≥1)				Recurren	it falls (≥2)		
Potentially associated factor	P _{rf} (%)	P _{nrf} (%)	OR	95% CI	P _{rf} (%)	P _{nrf} (%)	OR	95% CI
Age (≤57.7 ^b)		1			64.8	57.6	1.4	0.84-2.18
Acute infection + initial treatment outside EU, %			·		73.7	59.4	1.9	0.89-4.12
MMT lower limbs Sum score (≤64.5 ^b) (n=258)	83.1	67.9	2.3	1.28-4.22	67.8	55.0	1.7	1.03-2.87
Knee extension weakest leg (≤3 ^b) (n=270)	84.8	67.6	2.7	1.47-4.87	69.6	54.5	1.9	1.16-3.16
Orthosis	82.9	69.3	2.2	1.21–3.82	67.5	56.6	1.6	0.98-2.59
Physical complaints	C C F	r	0 7					
kigiaity joints and muscles Problems maintaining balance	/ 0.4 85.1	61.2	3.6	2.07-6.36	- 72.6	- 45,5	3.2	1.94-5.21
Reduced sensation legs	82.5	72.2	1.8	0.94-3.47	68.8	58.4	1.6	0.91-2.71
Back pain	77.8	70.2	1.5	0.87-2.57	64.9	54.8	1.5	0.93-2.49
Fear of falling	81.4	64.2	2.4	1.42-4.22	67.2	50.9	2.0	1.21-3.22
Total FES (≥5.5 ^b) (n=273)	83.4	64.8	2.7	1.55-4.83	71.0	50.0	2.5	1.49-4.04
Abbreviations: OR = odds ratio; CI = confidence interv All OR and 95% confidence intervals are uncorrected.	al; MMT = ma	nual muscle	testing; FE9	5 = falls-efficacy scale	ai			
r, The percentage of falls or recurrent falls in the pres. تربي The percentage of falls or recurrent falls in the abs	sence of the p	otentially ass otentially ass	sociated fac	tor. tor.				
The total number of people for whom information ak	out a variable	e was availabl	le is noted	behind each potenti	ally associated i	factor when it	differed fr	om the total (i.e.
289: 16 full-time wheel chair users removed).								

^b The continuous variables were transformed to dichotomous variables using their median values as cut-off points (median).

	Falls (≥1)		Recurrent	falls (≥2)
Potentially associated factor	Exp B	95% CI	Exp B	95% CI
Problems maintaining balance	3.42	1.87–6.25	3.01	1.78–5.08
Weakness knee ext. weakest leg (\leq 3)	2.66	1.42-4.89	1.88	1.11–3.18
Fear of falling	1.98	1.08–3.61	1.72	1.01-2.94

Table 6.6 Remaining predictor variables after stepwise binary logistic regression (n=270)^a

Abbreviations: Exp B: Expected B (\approx odds ratio), CI: confidence interval.

All OR and 95% confidence intervals corrected for multiple comparisons

^a n=270: 16 full-time wheelchair users removed and 19 missings for whom information on MMT knee extension was not available.

Discussion

This study shows that falls are a common problem among polio survivors and frequently lead to injuries, fear of falling and activity avoidance. The falls mainly occur during ambulation, inside the home and in the afternoon. Fear of falling, quadriceps weakness of the weakest leg and self-reported problems maintaining balance are independently associated with falls.

Falling is a problem: frequency and consequences

The rate of falling among polio survivors is high, with up to four times as many of our population than community-dwelling over-55 year olds falling once and one and a half times as many falling multiple times in the last year.^{15,21} Previous studies among polio survivors reported similar single fall frequencies (50–84%),^{5,11-13} but much lower recurrent fall frequencies (25%).¹¹

Negative consequences of falls were also frequent in our population. Four-fifths suffered an injury after a fall in the last year and one-fifth of these a major injury, two-thirds reported fear of falling and approximately a third of these had reduced their walking activity because of this fear. By comparison, community-dwelling older adults reported just over half the amount of major injuries (9%)¹⁵ and extremely varying percentages of fear of falls (21–77%).^{22,30,31} Unfortunately comparison with injury rates in large studies among polio survivors was not possible as these studies reported injuries over a longer time period (i.e. 5 years),^{13,14} but one small study reported similar fracture rates (i.e. 7% of fallers, n=1).¹¹ Levels of fear of falling and reduced walking activity were comparable to that reported previously¹¹⁻¹³ and as both variables are also risk factors for more falls, they may contribute doubly to the problem of falling of polio survivors.²²

Fall mechanisms: circumstances and associated factors

Knowledge of fall mechanisms can help target or create fall intervention strategies. Evaluation of the fall circumstances and factors potentially associated with falls in this group revealed some patterns that point to different fall mechanisms than in the elderly.

Most participants reported falls in the afternoon and during ambulation (mainly while walking), just as community-dwelling elderly do.^{32,33} It is possible that (muscle)fatigue is a contributor to these falls as in late polio, muscle load during normal daily activities can be close to the maximum muscle capacity, leaving little reserve for other activities later in the day.³⁴ Furthermore, in community-dwelling elderly, a larger proportion of elderly also report falls in the morning (30%) and at night (4%) than in our group.³² Most polio survivors fell in a familiar environment, presumably because more time was spent at home due to retirement or disability and because people concentrated less in familiar places. Interestingly, more falls occurred inside the home than just outside the home (40 and 10%, respectively), while the opposite seems true for older adults (23 and 35%, respectively).³² These findings emphasize the importance of removal of domestic hazards for fall prevention.

Three factors potentially associated with falls were found to indeed be independently associated with both falls and recurrent falls. These were: quadriceps weakness of the weakest leg, fear of falling and frequent complaints of problems maintaining balance. Those with quadriceps weakness (MRC \leq 3) had both single and recurrent falls more often than those with mild or no paresis (MRC >3). Pointing to muscle weakness as a likely risk factor for falls in polio survivors, although a longitudinal study is necessary to confirm this. That **knee extensors** seemingly play a more important role than other lower limb muscle groups in polio survivors is new and differs from previous research in polio survivors.⁵ As powerful knee extension is necessary for knee stability during the stance phase, weakness of the quadriceps could lead to knee buckling. Meanwhile, sufficient hip flexion and ankle dorsal flexion ensure foot clearance during the swing phase, thus failure of these muscles could lead to increased tripping and stumbling. It follows that knee buckling may be the most important fall mechanism in our group. However, as gait can be considerably altered by a variety of common problems in polio survivors (e.g. the distribution and severity of pareses, bone and joint deformations and contractures), failure of quadriceps strength should always be evaluated in the perspective of the individual's gait pattern. Further research into the role of the severity and location of muscle weakness in falls is necessary. The univariate association between orthosis use and falls can be explained by the underlying muscle weakness for which the orthoses were prescribed. Since muscle weakness was associated with falls despite orthosis use, it is questionable whether orthoses are effective tools for realizing the objective of more and safer mobility. Further research in necessary to elucidate the exact role of orthoses in causing falls since here, those who weren't wearing their orthosis during the last fall could not be distinguished from those whose orthosis caused the fall (e.g. increased risk of tripping). Fear of falling is both a consequence^{12,13,22} and a risk factor²² for falls and was independently associated with both single and recurrent falls in this study. Three of the four FES-items which caused the most concern irrespective of fall frequency involved walking (climbing stairs, walking around neighbourhood and going shopping), which was also the activity most frequently associated with falls. The variable 'self-reported problems maintaining balance' was the third factor independently associated with (recurrent) falls. The feeling of balance is determined by a variety of factors besides muscle strength including sensory input, range of motion and central nervous system functioning (e.g. vestibular apparatus and cerebellum). Perhaps, the perceived imbalance in our population can be (partially) explained by underlying problems of rigidity of joints and muscles and reduced sensation in the legs, as both were reported significantly more often among (recurrent) fallers than non-(recurrent) fallers. Although reduced sensation is not a classical symptom of polio,^{35,36} there is some evidence that polio survivors suffer from reduced proprioceptive input during muscle contraction due to altered sensibility of muscle spindles at different contraction levels.³⁷ Further clinical information on these possible sensory disturbances was unfortunately not available here, but future research on this topic would be valuable in order to clarify their role in causing balance disturbances and falls.

Among community-dwelling elderly medication use¹⁸⁻²¹ and increasing age^{15,21,38} are two risk factors for falls, that were not associated with falls in our population, but do deserve comment. The lack of a significant association between polypharmacy or the use of specific drug classes and (recurrent) falls, may be due to lack of power as the proportion that used multiple drugs and 'high risk' drugs was relatively low. It may still be important to assess medication use at an individual level. The majority of our group fell victim to the last major epidemic of polio in the Netherlands (1956) at a young age, resulting in a limited age range in the population (74% was between 50–70 years old), complicating statistical analyses. This may explain why we (and another study in a developed country)¹³ found no association between fall status and age.

Study strengths & limitations

A great strength of the study is the high response rate and the large sample size in combination with the diversity in severity of polio residuals of the participants. These features ensured that the population is representative for all polio patients who are referred to specialised centres. One limitation of this study is the potential recall bias, an unfortunate by-product of retrospective studies that may have led to an inaccurate description of the consequences and circumstances of falls and even an underestimation of fall incidence here (i.e. in a previous study among cognitively unimpaired over-60 year olds, 9% did not recall a fall they had experienced in the preceding year).³⁹ In order to maximize the accuracy of recall of the circumstances of falls, we asked for details of the most recent fall only. The sample size was sufficiently large to compensate for any extraordinary fall circumstances that may have been included due to this method. A second limitation is that due to the cross-sectional design of the study, causality cannot be established. Longitudinal studies are necessary in order to determine whether the factors we found to be associated with falls are in fact also risk factors for falls. A third limitation is the use of MRC sum-score retrieved from patient files. First of all, the use of MRC-scores recorded in the files automatically includes values measured by different physicians under different circumstances, inevitably involving interrater differences. Secondly, MRC-scores are a qualitative ordinal scale and as such the validity of a sum score is questionable. Thirdly, 38 patients had to be excluded from analyses with MRC sum scores due to incomplete data. Thus, lower limb MRC sum scores might not have reflected muscle strength with sufficient accuracy. Lastly, instead of including a control group we chose to compare our findings with the extensive literature on falls in the elderly, for whom successful fall interventions already exist. Although an own control group is always preferable, especially the comparisons with Stalenhoef et al. are very relevant as the questionnaires used were for a large part identical.¹⁵

In conclusion, falls are an important problem for polio survivors. The frequency with which falls occur and the severity of the consequences, merit the development of fall intervention strategies. As there are some essential differences between the fall mechanims in our group and those which have previously been described in the elderly, existing fall intervention strategies cannot simply be applied to this group. Tailor-made interventions are required and based on our findings these should focus on: increasing safety of walking and reduction of domestic hazards, reduction of fear of falling and on increasing muscle strength or stability where possible (especially of the quadriceps). Meanwhile, additional research is necessary

to elucidate the role of: orthoses, muscle weakness in the context of abnormal gait, sensory problems, fatigue and the possible causes of perceived loss of balance.

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Section D

Conclusions and future prospects

Chapter 7

General discussion

A large proportion of the estimated 10–20 million polio survivors worldwide can be expected to experience symptoms of further neuromuscular decline for many decades to come as they develop post-polio syndrome (PPS).¹ The lack of knowledge of pathophysiology and the unpredictability of the rate or extent of this continued decline creates challenges for the development of successful intervention strategies.²⁻⁴ For this reason, this thesis endevours to expand the knowledge in these areas. The aims are threefold:

- 1. To gain more insight into pathophysiological mechanisms underlying loss of muscle strength in PPS.
- 2. To assess the long-term rate of decline in physical mobility in relation to strength decline in PPS and to investigate potential predictors of the rate of deterioration of physical mobility in PPS.
- 3. To establish the magnitude and severity of the problem of falling, the circumstances of falls and associated factors in polio survivors in the context of their neuromuscular decline and physical mobility problems.

These aims led to several specific research objectives as discussed in the outline in **chapter 1**. The current chapter summarizes the main findings of this thesis and discusses the clinical implications thereof. Furthermore, important methodological aspects of the different studies are considered and recommendations for future research are given.

Main findings

Before a discussion of the possible causes and consequences of loss of strength in PPS can take place, the rate of strength decline in PPS in comparison to healthy ageing must be clear.

Strength decline

In our PPS-cohort of patients with a symptomatic decline of and neuromuscular transmission defects in the quadriceps, strength declined at a rate similar to that reported by previous studies that also included polio survivors without PPS (1–2.5% annually) (**chapter 2**).⁵⁻⁷ We therefore conclude that average rate of strength decline in PPS is moderate. Interestingly, our PPS-patients lost less strength over 10 years than the healthy controls did, both absolutely and relatively. In part, this can be explained by the higher baseline strength in controls, i.e. they have more to lose. It also suggests that muscles of PPS-patients suffer less from

sarcopenia. It has been proposed that many age-related muscle changes may be the result of a sedentary lifestyle, i.e. disuse.⁸⁻¹⁰ This idea comes from studies of ageing, high-level recreational athletes ("master athletes") who appear to be able to maintain their muscle strength and integrity throughout life through regular exercise.^{8,11} It is further supported by studies that found a great loss of muscle mass and strength as well as changes in blood flow, hormone levels and inflammatory protein expression after relatively short periods of bed rest.¹² In PPS-patients muscle mass is reduced,¹³ which means a greater proportion of the muscle will be used during activities of daily life. For example, rising from a chair in which the knees are flexed 90 degrees requires approximately 50Nm torque around each knee joint,¹⁴ and compensation by forward flexion of the trunk does not automatically reduce the load on knee extensors.¹⁵ 50Nm is a value close to or even higher than the maximal quadriceps strength measured in -the strongest leg of- some of our participants. Thus, this simple activity requires a relatively high load and consequently when performed may act as a training stimulus for the remaining muscle mass. We propose that the remaining muscle tissue of PPS-patients can best be compared to those of master athletes, and are maintained at an optimum through 'training' during every day activities. In support of this, muscle biopsy studies have found muscle fibre hypertrophy in PPS-patients, indicating considerable use of these remaining fibres.13,16

Pathophysiology

The pathophysiological mechanisms potentially underlying the strength decline in PPS were addressed in three chapters of this thesis. Prior to these studies, the most accepted hypothesis for the pathophysiology of strength decline in PPS – attrition of nerve endings¹⁷ – had not been confirmed in longitudinal studies.^{5,18-21} In **chapter 2** we demonstrated for the first time that MU size indeed declined over time in a group of patients with PPS, that the decline was greatest in the muscles with the largest remaining units, and that the rate of MU size decline was related to the rate of strength decline. Our study provided neurophysiological support for the hypothesis that axonal degeneration leads to strength decline. Together with evidence ascertaining further loss of whole motor units later in life in polio survivors^{5,22,23} this forms a firm foundation for the theory that denervation underlies loss of strength in PPS.

At a muscular level, denervation leads to pathological muscle changes in the form of fatty invasion, fibrotic transformation, and atrophy, as had been shown in biopsy studies.^{13,18} In **chapter 3** we visualised these pathological changes using muscle ultrasound and found

that the lower strength in PPS-patients was reflected by significantly lower muscle quality (fatty invasion and/or fibrotic transformation) and quantity (atrophy) compared to healthy controls. Moreover, there was a clear relationship between these pathological muscle changes and muscular dysfunction in PPS-patients as the degree of muscle quality and quantity correlated to the degree of strength remaining. Muscle ultrasound therefore provides a quick and relatively simple way of visualising the changed muscle architecture, which previously was only possible with more expensive and complex techniques such as CT and MRI. Because our study consisted of a one time measurement it is however not possible to distinguish the muscular changes that occurred directly following acute poliomyelitis from those that appeared later, as part of PPS.

Neuromuscular adaptations

The body can respond to denervation in several ways in an attempt to maintain strength. First, at a muscular level, remaining muscle fibres may hypertrophy in response to the increased load. This indeed appears to happen in PPS-patients, evidenced by large mean fibre areas in biopsies of symptomatic muscles¹³ and even entire muscle hypertrophy in some (chapter 3). Second, an increased ability to activate the available muscle mass could lead to more efficient use of the remaining tissue. In PPS, there is varying evidence that the opposite happens, with studies finding a reduced ability to activate the muscles in selected patients and muscles and a normal ability in others.^{18,24-28} Third, at the motor neuron level, MUs with recent loss of distal axons have a certain capacity for distal axonal sprouting to counteract the denervation. Also, neighbouring MUs have the ability to re-innervate orphaned muscle fibres, within certain anatomical constraints (e.g. within a fascicle and across a limited distance). It is known that both mechanisms are active during the recovery phase after acute polio, resulting in (a degree of) strength recovery.^{17,29,30} There is also evidence for continued re-innervation in older polio survivors in the form of increased jitter on single fibre EMG. Increased jitter suggests ongoing de- and reinnervation resulting in an unstable synapse with abnormal neuromuscular transmission.^{29,31} All of our cohort at baseline had increased jitter.²⁴ Together with the increase of average MU-size over time in some individuals in our study (chapter 2, Figure 2.3), this suggests there is still active ongoing re-innervation in PPS-patients. Yet, this mechanism failed to counteract the rate of denervation in the largest proportion of our PPS-patients, as overall there was a decline in MU-size. In conclusion, our findings added to previous studies indicate that many adaptive mechanisms at muscular, end plate, and motor neuron level are still present in PPS-patients. Yet, these compensation

strategies are not enough as average MU-size and strength decline over time (**chapter 2**). The interplay of these different mechanisms, which may be present or absent to varying degrees in each individual, added to the wide variety of residual paresis/denervation after acute polio, might explain the great differences between PPS-patients. This in turn makes it difficult to predict the rate of decline for each individual PPS-patient.

Inflammation as a cause of PPS

There are several possible explanations for the attrition of nerve endings in PPS shown in chapter 2. The most accepted is the 'overuse' or 'metabolic theory', which assumes there is a limit to how long a motor neuron can sustain the increased metabolic demands required by its increased size.¹⁷ More recently, the 'inflammatory theory', which postulates an ongoing inflammatory process further compromising the already overfunctioning motor units, has gained traction.³¹⁻³⁴ We found some evidence for this theory, as several pro-inflammatory mediators were elevated systemically in PPS-patients compared to healthy controls (chapter 4). Added to previous reports of signs of inflammation in spinal cord, muscle, serum and CSF these findings suggest immune dysregulation does indeed play an important role in PPS.³³⁻⁴³ However, we did not find any evidence of a relationship between immune mediator levels and denervation or strength decline over time. Theoretically, inflammation could lead to muscle atrophy in several ways. First, inflammation localised in the CNS could result indirectly in loss of muscle tissue through denervation. This is the main theory that has been studied so far in PPS, with varying results. Multiple studies have found raised expression of inflammatory markers in CSF, but while lowering these levels through IVIG treatment is possible,³⁶ a meta-analysis of randomized controlled trials with IVIG found no evidence for effect on clinical outcomes.³ Second, inflammation could act directly at a muscular level. There is some evidence for this in polio survivors as some studies have found lymphocytic infiltrates in symptomatic muscles and higher expression of enzymes of the prostaglandin E2 synthetic pathway, indicative of local inflammation.^{41,44} In other chronic disease states involving muscle atrophy, skeletal muscle also shows increased expression of pro-inflammatory mediators.⁴⁵ This has not yet been studied in PPS-patients, but if present it would allow increased local catabolic action of these mediators. Therefore, it currently remains unclear whether the inflammation found represents the primary pathogenic process underlying PPS or is an epiphenomenon with no causal role in the symptomatology.

PPS versus normal aging

Considering the findings described in chapter 2–5 of this thesis and the evidence in PPS literature so far, the question arises whether PPS represents a separate disease process or is akin to early onset of 'normal ageing'. There are indications that all levels of adaptations taking place in PPS-patients as discussed above are to some extent also present in 'normal' ageing. 1) At a muscular level, there is a loss of type 2 muscle fibres and fibre-type 1 grouping,⁴⁶ 2) at a nerve level, there is denervation in the form of a loss of motor units,^{22,46} instability of the neuromuscular junction and enlargement of surviving motor units⁴⁶ and 3) at systemic level, there is evidence of increased inflammation – among others high levels of circulating IL-6 and TNF-alfa – which is considered to be a significant contributor to the age-related muscle wasting process.^{12,47,48} On the other hand, the argument that sarcopenia is mainly the result of disuse does not fit with our findings suggesting that PPS muscles are more comparable to those of master athletes than those of sedentary elderly (chapter 2). Even if PPS were shown to be a form of early ageing, the extensive neuromuscular adaptations and loss of strength in this group remain an important issue for affected patients. A 50 year old with muscle strength of an >80 year old will be severely limited as the physical demands on a younger person are greater. To what degree physical functioning is affected in PPS and how this relates to loss of muscle strength was studied in the remaining chapters of this thesis.

Physical mobility problems

In **chapter 5** we showed that deterioration of physical mobility of PPS-patients is moderate, declining with an average 2 minute walking distance of 7m (or 6%) over 10 years. A comparable rate of decline to that found in other studies including people without symptoms of PPS.^{7,49,50} Recently, normative data for the 2 minute walk test was collected cross-sectionally from a large (n=1,137) population-based sample of healthy volunteers.⁵¹ Comparison of our PPS data to that of these healthy peers reveals that the PPS cohort had a distinctly lower average walking speed both at baseline and follow-up and more inter-individual variability (Table 7.1).

This difference moreover persists to great age so that the average walking distance for 'healthy' 80 to 85 year olds is still remarkably higher than that of 50–60 year old PPS-patients. So despite the moderate rate of decline in walking capacity in our PPS-patients, their limitations herein are equal to those of people many decades older. The increasing disability posed by decreased walking capacity in PPS-patients was emphasised by increased use of walking aids and a shift to walking aids offering more support (**chapter 5**).

	Age (years)	Distance walked, m (95% CI)
PPS baseline	52±8	120.3 (71.7–168.9)
PPS follow-up	62±8	113.6 (97.2–174.6)
Norm data ^b	18–54ª	192.0 (180.8–204.6)
Norm data ^b	60–64	172.8 (158.2–192.8)
Norm data ^b	80–85	139.2 (125.7–155.6)

Table 7.1 The 2 minute walk test, a combination our data (chapter 5)⁵² and norm data⁵¹

^a Authors report analysis of variance (controlling for sex) showed no difference in the 2 minute walk test distance between age groups 18 and 29, 30 and 39, 40 and 49, and 50 and 54 years.⁵¹ For this reason, the comparison between this group and our patients is valid despite its broad age range. ^b The norm data presented here is a combination of the male and female data from Bohannon et al.⁵¹

About one fifth of the cohort experienced a much greater decline than the rest over 10 years, prompting further investigation into whether these people could have been identified earlier. This faster degree of deterioration could not be predicted from baseline strength and overall only 11% of the variation in decline in walking capacity could be explained by the decline in quadriceps strength (chapter 5). In part, this weak correlation might be explained by our use of strength measurements of just one lower limb muscle rather than a combined measure of multiple muscles. However, this muscle is a key muscle in ambulation and its strength has been found to correlate strongly with distance walked in 6 minutes cross-sectionally.⁵³ Our study was the first to compare long-term changes in the two parameters in PPS-patients and another more recent study of the relationship between knee muscle strength, gait performance and physical activity came to similar conclusions.⁵⁴ These findings demonstrate that additional factors must influence walking capacity. Several possibilities are the overall severity and distribution of muscle weakness, osteo-articular changes, use of walking aids, co-morbidity and personal and environmental factors. First, the degree to which each muscle is affected by polio varies widely among the victims⁵⁵ and there is some evidence that the overall extent of paresis predicts reduction in self-reported physical mobility and or functional independence over time.^{7,56} Second, asymmetrical bone growth in childhood, joint deformities, and osteo-articular operations are frequent occurrences in polio survivors that often lead to asymmetrical muscle and joint loading, increased osteo-articular degeneration and alterations in gait patterns.⁵⁷⁻⁵⁹ Third, use of walking aids and orthoses to compensate for these changes generally lead to safer, but not necessarily faster gait.^{57,59,60} Fourth, people do not automatically adapt their walking speed to their decreasing abilities.⁶¹ People tend to have a preferred walking speed relative to the
energy cost of walking to reduce feelings of fatigue during walking.^{62,63} There is increasing evidence that gait asymmetry is in itself energy consuming and might therefore invoke a reduction in walking speed to reduce the energy cost.⁶⁴ However, the preferred speed is also governed by various personal and environmental factors, such as a desire to keep up with peers (or in the laboratory setting to 'score highly' on the test), a need to move quickly (e.g. cross the road), physical fitness and fear of falling. Finally, co-morbidity, a prevalent problem in polio survivors,⁶⁵ may have an effect on walking capacity as well. Stolwijk-Swüste et al., found an impact of comorbidity on the course of functional independence over 5 years in polio survivors.⁷ It is certainly possible that changes in walking capacity are likewise affected by co-morbidity. In our study, all these additional factors potentially influencing walking capacity were most likely present to some degree. Investigating the predictive value of these different potential factors would be an interesting field for future research.

Falls

In **chapter 6** we confirmed that falls are an important problem for polio survivors with and without PPS. The fall incidence in our group (74% last year) was considerably (up to 4 times) higher than that reported by adults of similar ages without chronic physical disabilities⁶⁶ and also many fell repeatedly (60%). This is in line with studies published before and since (50–84%).⁶⁷⁻⁷³ Among older adults falls have been found to lead to higher rates of mortality, morbidity and loss of functional independence,^{74,75} resulting in high costs for the individual, society and the health care system.⁷⁵ In polio survivors there is also a serious amount of morbidity related to falls, with many reporting minor and major injuries, fear of falling and subsequent reduction of walking activity.^{68,70,76,77} The latter finding especially is likely a risk factor for a further reduction in functional independence in this group as well as for a faster rate of decline following a more sedentary lifestyle. From our data we conclude that frequency of falling is so high and the consequences so severe, that all polio survivors should be considered at risk for falls and assessed accordingly.

Together these findings offer a compelling argument to ensure fall risk assessments and intervention programmes become available for polio survivors. A multitude of fall intervention programmes have been developed for elderly people, with varying degrees of success.⁷⁸⁻⁸² The most successful programmes are multifactorial and many start with a systematic risk assessment in order to determine which risk factors are contributing to the increased fall rate in each individual, so that these can be targeted in consequent steps. In our cohort of polio survivors fear of falling, quadriceps strength, and problems maintaining balance were associated with higher fall incidence (chapter 6). In addition, most falls occurred in the afternoon, during ambulation and in the home, suggesting a role for (muscle) fatigue and environmental factors. In more recent studies, age, self-reported vision problems, and leg length discrepancy were found to be risk factors for falls in PPS patients, while the importance of knee-extensor strength was called into question.^{71,73} Also, these studies confirmed most falls occurred during ambulation and in the afternoon, although in both slightly more people fell outside than at home, perhaps indicating a different life-style. All these factors then, should be the principal focus of a fall risk assessment in polio survivors. However, separate from the risk factors specific to polio, 'normal' risk factors for falls cannot be ignored as this population is also ageing – e.g. co-morbidities, polypharmacy, cognition, depression, etc. After a personalised risk inventory has been taken, the next step would be an intervention programme to reduce the influence of each risk factor. So far, these do not exist specifically for polio survivors and those used for elderly are often not applicable. The mainstay of these interventions is generally strength training and/or endurance training.^{78,82} While decreased muscle strength is a factor associated with falls in polio survivors, it is as yet uncertain to what degree exercise training is effective in counteracting loss of strength in this group.^{3,83} Separate from this issue, a key impediment to participation in these standard fall interventions will be the extensive use of orthoses and walking aids by polio survivors. These preclude participation in essential parts of most existing interventions in their current form (e.g. obstacle courses, fall training or tai chi).78,84

Methodological considerations

Study population

This thesis involved two separate study populations, one broad population of polio survivors with and without the diagnosis PPS and with or without symptoms of decline, and a second homogenous population of PPS-patients with symptomatic quadriceps dysfunction with proven neuromuscular transmission defects. Each of these groups offered a specific research advantage. In order to investigate the incidence, circumstances and consequences of falls we wanted a broad population with much diversity of polio residuals and complaints in order to discover the most relevant and generalizable factors related to falls (**chapter 6**). Meanwhile, for the studies into the pathophysiology and long-term decline it was most important to have

a diagnostically homogenous group to be able to identify specific neuromuscular changes, while limiting variability (**chapter 2–5**). The choice of the homogenous group may have limited the generalizability of the results, but did allow us to draw some important conclusions as to the pathophysiology of PPS, which would otherwise not have been possible.

Longitudinal measurements

The nature of PPS as a slowly progressive disease means that a long follow-up period is necessary in order to determine with any certainty what degree of clinical deterioration has taken place.^{85,86} A particular strength of the longitudinal measurements described in this thesis is that they spanned 10 years, an exceptionally long follow-up period, and that a relatively large number (~71%) of the original participants were available for follow-up (**chapter 2, 4 and 5**). A limitation herein is that no measurements were taken within the follow-up period. The addition of extra measures to the baseline and 10 year data would have allowed a better estimation of the time course of the disease and of the role of the potentially influential factors on this time course.

In **chapter 2**, a particular complication of the long follow-up period was technological advancement of EMG analyses that had taken place in that time. This necessitated reanalyses of the initial EMG data to ensure comparable outcome measures. Although time consuming, this re-analysis means we can be assured of the accuracy of our results. Because of the long-term follow-up it is likely that lifestyle changes have also taken place, such as people retiring (resulting in a change in physical and mental demands), or a reduction or increase in exercise over time. Although it was not possible to quantify or correct for all these potential confounders, the inclusion of an age- and gender matched control group should have reduced the effect of such confounders, since these people also aged 10 years over the same period.

Outcome measures

The relevant benefits and limitations of our chosen outcome measures were discussed in each individual chapter. Only those points not previously discussed or judged important for multiple studies from the thesis will be highlighted here.

A potential limitation of the studies involving EMG and ultrasound measurements (i.e. **chapter 2 and 3**) was that we studied only the vastus lateralis muscle in relation to qua-

driceps strength, while the degree of damage from polio may vary between the four heads of the quadriceps that determine knee extension strength. Studying all four heads of the quadriceps, or better still multiple lower limb muscles bilaterally, would have allowed a more comprehensive study of the relationship between MU-size and strength (**chapter 2**), ultrasound parameters and strength (**chapter 3**), inflammatory mediator levels and strength (**chapter 4**), and physical mobility and strength (**chapter 5**).

The within-subject variation in strength and walking capacity measurements – used in **chapters 2–5** – are known to be high in healthy subjects and even higher in PPS-patients.^{85,86} At a group level, the reproducibility of these two outcome measures was sufficient to use reliably in the 10 year longitudinal study (smallest detectable change 4.5% for strength and 3m for walking capacity). The large measurement error of these outcome measures does however complicate investigations into the relationship between strength and physical mobility.

We investigated a great number of potential risk factors for falls in **chapter 6** of this thesis, thereby revealing some important topics for future research into fall intervention strategies. A shortcoming of this study is that it was cross-sectional which did not allow conclusions to be drawn about causality and that it did not include any standardised physical tests as it was a questionnaire and patient file based study.

Clinical implications

Patient counselling

If a polio survivor visits the outpatient department with complaints of a decline in physical mobility or strength, it is important to first assess whether other potential causes of rapid declines are present.⁸⁷ Once ruled out, the fear of rapid declines that some patients have can be dispelled using the knowledge obtained in this thesis, i.e. that strength and physical mobility decline at a modest rate (**chapter 2 and 5**). In addition, the explanation that the loss of strength is (at least in part) the result of loss of motor neurons and distal axons of motor neurons and that there is evidence of systemic inflammation may help people better understand what is happening to them (**chapter 2 and 4**). Ultrasound measurements are a quick and non-invasive method to help visualise the muscular changes and might be used in a clinical setting, as a cheaper and faster alternative to MRI, to improve people's understanding of these underlying processes (**chapter 3**). Overall, improved knowledge of

the pathophysiology and prognosis allows for a better counselling about the importance of avoiding over- and underexertion of muscles. Also, it might help encourage people's acceptance of appropriate (mobility) aids or compensation strategies in order to continue participating in activities that are important to them.⁸⁸ Additional counselling about the high rate of falls among polio survivors, even when this is not the main reason for the consult (**chapter 6**), may help people be more aware of potential risk factors and take measures to prevent falls or seek help if falls occur frequently.

Assessing change

Because of the large degree of individual variation found in all of our studies (chapter 2-6) and lack of predictive factors for a faster rate of decline (chapter 5) it is important that polio survivors who experience new symptoms are monitored at regular intervals to assess the rate of decline. Considering the natural course of the disease generally involves a moderate rate of decline (chapter 2 and 5), yearly or two yearly monitoring should be sufficient, and the frequency can be reduced if little changes over time. Such an examination should at least consist of a detailed history taking (including all the known secondary consequences of polio and self-reported decline in physical mobility), measurements of strength of functionally important muscles, balance and physical mobility, and if possible baseline MRI scans or ultrasound measurements to identify affected muscles. Potentially, muscle ultrasounds measurements could also gain a valuable place in the follow-up measurements (chapter 3 and see future research). Apart from this general assessment focussed on detecting (rate of) decline, it is important that such an examination also focus on the presence of fall risk factors, even in those patients who have not yet experienced falls (chapter 6). Such an assessment should at least include questions about recent falls (in the last year) as well as all the potential risk factors identified in this thesis and in more recent studies,^{71,73} i.e. fear of falling, quadriceps strength, problems maintaining balance, muscle fatigue, environmental factors, vision problems, and leg-length differences. Where appropriate, a standardised assessment of clinical tests can be added to further identify specific risk factors for falls in individual patients. The goal of such monitoring should at all times be to provide effective, individualised interventions at the right time.

Interventions

So far, exercise programmes, cognitive therapy and medications have not proven effective at reducing fatigue or improving strength or functioning.^{3,83,89} Therefore at this point, available interventions aimed at improving physical mobility and preventing falls are based on clinical experience and can involve anything from orthosis and/or walking aid prescription, to gait and balance training, prescription of pain medication, psychological interventions, or referral to other specialists (e.g. for orthopaedic interventions). The most important contribution of this thesis in this area is that the great variation within the PPS-patients and polio survivors necessitates individualised care.

At this point in time, the finding of elevated levels of inflammatory markers in PPS-patients does not have any direct clinical consequences as there is not yet any evidence for a link between the immunological findings and symptoms of the disease (**chapter 4**). Then again, Swedish insurance companies are already paying for immunoglobulin treatment in PPS-patients based on the studies so far and a big international clinical trial is currently underway to determine effects of immune-modulating therapy in PPS (FORCE study⁹⁰). So it is possible, that there will be treatment options in this area available in the foreseeable future.

Future perspectives

Several recommendations for future research are forthcoming from this thesis. First, a longitudinal study measuring both MU number and MU size in relation to strength in PPS-patients, would be a valuable addition to current research in this field. It would allow for more in-depth analysis of the changes in innervation and of the extent to which these changes explain strength changes over time. If faster non-invasive EMG analysis techniques were developed one could even imagine them being applied as a clinical measure to assess changes in innervation of a particular muscle. Such a measure could also be useful in other patient groups with motor neuron disorders, such as ALS or SMA.

Second, muscle ultrasound is a promising technique which could potentially be used to measure disease severity, differentiate healthy and affected muscles within the same person, or capture changes resulting from disease progression or intervention in patients with different diseases (i.e. neuromuscular or motor neuron diseases). Before it can be used as measure of disease severity however, it would have to be determined experimentally which muscles are most relevant to each diagnostic subgroup of NMD and should therefore be included in a

standardised assessment. Also, longitudinal studies are required in order to establish which degree of changes in muscle architecture are considered relevant, how sensitive ultrasound is to detect these changes, and how they relate to changes in muscle function (i.e. strength). If this evidence becomes available, muscle ultrasound could be a useful tool in both trials and clinical practice. Moreover, as it is a cheap and relatively simple technique, it also has the potential to be used in low-income countries where poliomyelitis has only recently been eradicated (or where this is still pending) and thus most new cases of post-polio syndrome can be expected to occur.

Last, the absence of an applicable evidence based fall intervention programme for polio survivors is a crucial shortcoming in current patient care. As shown in this thesis, falls were more prevalent in polio survivors than in 'healthy' elderly populations, where much time and resources have been spent on developing fall intervention programmes. Yet, as discussed in the 'main findings' section above there are numerous impediments to enrolling polio survivors in these existing programmes. The development and efficacy testing of a modified programme would be a valuable area for future research. As such a programme must be tailored to be adaptable for use by people with progressive, asymmetrical loss of muscle strength, osteo-articular changes, and those who use mobility aids, it may also be useful in people with other diseases involving these problems (e.g. neuromuscular disorders).

On a more global scale, it is important to focus on sharing our acquired knowledge on postpolio syndrome with the countries where recent polio cases have occurred. Understandably, most of these countries are currently still focussed on eradication of acute polio instead of in investing in the futures of those who survived. The problems polio survivors in these countries face will in part be different to those faced in the west due to societal and political differences. For instance, more recently unvaccinated children are mainly poor, girls, and from remote areas.² These groups are not only more susceptible to poliomyelitis infection, but also have limited access to medical care and rehabilitation services if they do contract polio. International discussion platforms could help translate the many research findings from the developed world into forms that are relevant for the situation in the developing world. The most plausible way of achieving such communication would be a global (online) network for sharing information. If realised, current research findings in polio survivors will still be relevant for many decades to come.

In conclusion, the increased knowledge of pathophysiology, imagery thereof, and rate and extent of the continued neuromuscular decline accumulated in this thesis can help PPS-

patients better understand the origin of their symptoms and influence their acceptance of rehabilitation interventions. The findings of moderate, yet highly variable, and unpredictable rates of decline in physical mobility and frequent falls in this population moreover indicate the importance of individualised monitoring and care. Examples of which are given in this thesis. Challenges for the future involve improving longitudinal assessment capabilities with muscle ultrasound, developing appropriate fall interventions, and initiating and maintaining global knowledge platforms for sharing information about post-polio.

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Chapter 8

Summary

Pathophysiology of muscular changes in post-polio syndrome and consequences for physical mobility

A large proportion of the estimated 10–20 million polio survivors worldwide can be expected to experience symptoms of further neuromuscular decline for many decades to come as they develop post-polio syndrome (PPS). **Chapter 1** in **Section A** contains an overview of the insights into PPS as they stood at the start of this thesis. It describes how the lack of knowledge of pathophysiology and the unpredictability of the rate or extent of the continued decline in PPS creates challenges for development of successful intervention strategies. This thesis endeavours to expand the knowledge in these areas. **Section B** focusses on the pathophysiology of muscle changes in PPS, in particular of muscle weakness, and **Section C** on physical mobility problems in relation to muscle weakness in polio survivors.

Section B: Pathophysiology of muscular changes in PPS

Prior to the studies described in this thesis, the most accepted hypothesis for the pathophysiology of strength decline in PPS – i.e. attrition of nerve endings – had not been confirmed in longitudinal studies. In **chapter 2** we addressed this issue in a long-term prospective cohort study among 47 PPS-patients with symptomatic quadriceps dysfunction and transmission defects on single-fibre EMG and 12 healthy controls. We demonstrated that quadriceps strength and average motor unit (MU-)size indeed declined in PPS-patients (by 15% and 20% over 10 years, respectively) and that those muscles with the largest units at the start exhibited the greatest losses of mean MU-size and proportional decreases in quadriceps strength over time. Controls lost 29% of strength over 10 years, without any change in MU-size, indicating a different underlying mechanism for strength decline. We proposed that the smaller loss of strength in PPS-patients than in controls might suggest that muscles of PPS-patients suffer less from sarcopenia. Overall, this 10-year longitudinal study provided neurophysiological evidence for the attrition of nerve endings in PPS and support for the hypothesis that denervation leads to strength decline.

At a muscular level, denervation can lead to changes in muscle architecture through fatty invasion, fibrotic transformation, and atrophy of muscle fibres. This loss of normal muscle anatomy might in turn explain the loss of strength. In **chapter 3**, we showed that the reduced quadriceps strength of PPS-patients was indeed reflected by a significantly lower muscle quality (more fatty invasion or fibrotic transformation) and quantity (more atrophy)

compared to the healthy controls as measured by muscle ultrasound. In this cross-sectional study, among the same participants as in **chapter 2**, we found muscle ultrasound was not only capable of distinguishing muscles of healthy participants from those with PPS, but also that the degree of muscle quality and/or muscle quantity correlated to degree of strength in the PPS-group. Thus, this technique could potentially be used to differentiate affected and non-affected muscles within the same person. Also, if proven sensitive longitudinally, ultrasound measurements might be useful as an objective follow-up measure for muscle function, since the technique is not impeded by the frequent and variable symptoms of PPS (e.g. joint/ muscle pain) in contrast to strength measurements.

One hypothesis for why denervation and muscle fibre changes might take place in PPS is the inflammatory hypothesis which postulates an underlying chronic systemic inflammatory process. In chapter 4 we found evidence for systemic inflammation in PPS, yet this was not related to clinical deterioration over 10 years. Plasma levels of 4 pro-inflammatory and immune modulatory mediators (i.e. TNF-a, IL-6, IL-8, and leptin) were significantly increased in PPSpatients with symptomatic quadriceps dysfunction compared to levels in healthy controls. Moreover, 51% of PPS-patients had elevated levels of 4 or more inflammatory mediators, compared to 22% of controls. Added to previous reports of signs of inflammation in spinal cord, muscle, serum and CSF these findings suggest immune dysregulation does indeed play an important role in PPS. There was however no association between these raised systemic levels of inflammatory mediators and long-term decline in MU-size, quadriceps strength or other clinical parameters. Yet, our findings do not preclude a role for these mediators in PPS symptomology as the effective concentration locally (in the CNS and muscle fibres) may deviate from the systemic concentrations. Therefore, while in other chronic diseases systemic inflammation has been linked to muscle wasting, in PPS the relationship between observed systemic inflammation and clinical deterioration remains tenuous.

Section C: Physical mobility problems in polio survivors

We hypothesised that the progressive muscle weakness in combination with other common symptoms of PPS, such as joint problems, muscle pain, and fatigue, would progressively limit physical mobility and result in frequent falls in polio survivors.

In the study described in **chapter 5**, we found that average physical mobility of PPS-patients declined modestly over 10 years, with observed walking capacity declining by 6% and self-

reported mobility by 14%, in the same cohort that experienced 15% reduction of quadriceps strength in this period (chapter 2). The decline was further reflected by increased use of walking aids and a shift towards types of assistive devices that offer increased support. While the finding of modest declines should be reassuring for most patients, a fifth of the group experienced a substantial decline in walking capacity (27%) and self-reported mobility (38%) over the same period. Loss of quadriceps strength only explained a small proportion of the variance of the decline in walking capacity (R = 11%) and the rate of decline could not be predicted from baseline parameters. The individual variability combined with the lack of predictive factors underscores the need for careful monitoring of individual functional decline, preferably with objective measures (e.g. ultrasound measurements, chapter 3) and for personally tailored care based on actual functional decline in patients with post-polio syndrome.

In the survey based retrospective cohort study in **chapter 6**, we confirmed among 305 participants that falls are an important problem for polio survivors with and without PPS, as they occur frequently (74% \geq 1 fall in the last year; 60% \geq 2 falls) and cause many injuries (16% of fallers had major, and 64% had minor injuries). Also, fear of falling was widespread in this cohort (63%) and almost a quarter (23%) of participants reported reducing their walking activity as a consequence. This fear, along with the quadriceps strength of the weakest leg, and problems maintaining balance, were independently associated with higher fall incidence in polio survivors. Most reported falls in a familiar environment (86%), during ambulation (72%) and in the afternoon (50%). The high rate of falls and consequences thereof, merit the implementation of fall intervention strategies. To maximize effect, they should be tailormade and target the fall mechanisms specific to polio survivors.

Chapter 7 summarizes the main findings and methodological considerations of this thesis and discusses the clinical implications thereof. This includes suggestions for how the results might be used to improve patient counselling and existing methods for monitoring change in strength and physical functioning. Finally, several recommendations for future research are presented. Among others we propose further investigation with muscle ultrasound in order to assess longitudinal assessment capabilities, the development of specific fall intervention strategies to reduce the problem of falling in PPS, and initiating and maintaining global knowledge platforms for sharing information about post-polio with the countries that are likely to need it most in the future.

Chapter 9

Samenvatting

Pathofysiologie van spierveranderingen in postpoliosyndroom en gevolgen voor fysieke mobiliteit

Wereldwijd leven naar schatting 10 à 20 miljoen mensen met de gevolgen van polio. Een groot aantal van hen zal de komende decennia een verdere achteruitgang van neuromusculaire functies ervaren als gevolg van het postpoliosyndroom (PPS). **Hoofdstuk 1**, in **Sectie A**, bevat een samenvatting van de inzichten in PPS zoals bij aanvang van dit proefschrift bekend was. Het beschrijft hoe het gebrek aan kennis over de pathofysiologie en de onvoorspelbaarheid van de mate en snelheid van achteruitgang in PPS belemmerend is voor de ontwikkeling van interventiestrategieën. Het doel van dit proefschrift is om de kennis over de pathofysiologie en het beloop van PPS te vergroten. **Sectie B** richt zich op de pathofysiologie van spierveranderingen in PPS – zich met name uitend in spierzwakte – en **Sectie C** op problemen met fysieke mobiliteit en hoe deze zich verhouden tot spierzwakte in mensen met doorgemaakte polio.

Sectie B: Pathofysiologie van spierveranderingen in PPS

Een degeneratie van de zenuwuiteinden was voorafgaand aan dit proefschrift de meest geaccepteerde hypothese voor de pathofysiologie van spierkrachtverlies in PPS. Longitudinale studies hebben deze hypothese echter nooit bevestigd. In hoofdstuk 2 hebben wij deze hypothese onderzocht in een lange termijn prospectieve cohortstudie onder 12 gezonde proefpersonen en 47 PPS-patiënten met symptomatische quadricepsdysfunctie en transmissiedefecten bij single-fibre EMG-onderzoek. We toonden aan dat de quadricepskracht en de gemiddelde motor unit (MU-) grootte inderdaad afnamen in PPSpatiënten (met respectievelijk 15% en 20% over 10 jaar) en dat de spieren met de grootste MUs aan het begin van de studie, na 10 jaar de grootste afname in MU-grootte en in kracht lieten zien. Gezonde proefpersonen daarentegen verloren 29% van hun kracht gedurende 10 jaar zonder veranderingen in MU-grootte, wat erop wijst dat bij hen vermoedelijk andere mechanismen ten grondslag liggen aan het krachtverlies. Wij opperden dat het geringere krachtverlies in PPS-patiënten dan in gezonde proefpersonen suggereert dat spieren van PPSpatiënten minder bevattelijk zijn voor sarcopenie. Concluderend levert deze 10 jaar durende longitudinale studie neurofysiologisch bewijs voor de degeneratie van zenuwuiteinden in PPS en ondersteunt zij de hypothese dat de krachtsafname bij PPS het gevolg is van denervatie.

Op spierniveau kan denervatie leiden tot veranderingen in de structuur van de spier door infiltratie van vet- en bindweefsel en atrofie van spiervezels. Deze veranderingen in spieranatomie kunnen op hun beurt de krachtafname die optreedt bij PPS mogelijk verklaren. In hoofdstuk 3 toonden we met behulp van spierechografie aan dat de verminderde quadricepskracht van PPS-patiënten inderdaad werd weerspiegeld door een significant lagere spierkwaliteit (meer vet- en bindweefselinfiltratie) en spierkwantiteit (meer atrofie) in vergelijking met gezonde controles. In deze cross-sectionele studie, onder dezelfde proefpersonen als in **hoofdstuk 2**, vonden we niet alleen dat met spierechografie succesvol onderscheid kon worden gemaakt tussen spieren van gezonde proefpersonen en die van PPS-patiënten, maar ook dat de spierkwaliteit en -kwantiteit in de PPS-groep samenhang vertoonden met de mate van spierkracht. Derhalve zou de techniek potentieel gebruikt kunnen worden om aangedane en niet-aangedane spieren binnen dezelfde persoon te onderscheiden. Als echografie longitudinaal gevoelig blijkt te zijn voor veranderingen, zou het ook een betrouwbare objectieve methode kunnen zijn om de spierfunctie in de tijd te vervolgen. De metingen worden immers niet beïnvloed door frequent voorkomende en variabele symptomen van PPS (zoals spier- en gewrichtspijn) die krachtmetingen wel kunnen beïnvloeden.

Een hypothese voor het ontstaan van denervatie en de veranderingen in spierstructuur bij PPS is de ontstekingshypothese. Daarin wordt verondersteld dat een chronische systemische ontsteking ten grondslag ligt aan deze veranderingen. In hoofdstuk 4 vonden we wel bewijs voor een systemische ontsteking (inflammatie) in PPS, maar dit was niet gerelateerd aan de klinische achteruitgang gedurende 10 jaar. Plasmaspiegels van 4 pro-inflammatoire en immuun-modulerende mediatoren (d.w.z. TNF- α , IL-6, IL-8, en leptine) waren significant verhoogd in PPS-patiënten met symptomatische quadricepsdysfunctie in vergelijking met gezonde controles. Tevens had 51% van PPS-patiënten verhoogde spiegels van 4 of meer ontstekingsmediatoren, terwijl dit slechts bij 22% van de gezonde proefpersonen voorkwam. Samen met eerder gerapporteerde tekenen van ontsteking in ruggenmergweefsel, spierweefsel, serum, en hersenvocht suggereren deze bevindingen dat ontregeling van het afweersysteem inderdaad een belangrijke rol speelt bij PPS. Er was echter geen associatie tussen de verhoogde systemische spiegels van ontstekingsmediatoren en de lange termijn achteruitgang in MU-grootte, quadricepskracht, of andere klinische parameters. Toch sluiten onze bevindingen niet uit dat deze ontstekingsmediatoren alsnog een rol spelen in PPS-symptomatologie aangezien de lokale concentratie (in het centraal zenuwstelsel en in spiervezels) kan verschillen van de systemische concentratie. Wel is het zo dat, terwijl

in andere chronische ziekten is aangetoond dat systemische inflammatie gerelateerd is aan spierverval, de relatie tussen de geobserveerde systemische ontsteking en klinische achteruitgang in PPS vooralsnog onzeker blijft.

Sectie C: Problemen met fysieke mobiliteit in patiënten met doorgemaakte polio

De hypothese was dat progressieve spierzwakte in combinatie met andere veelvoorkomende symptomen van PPS, zoals gewrichtsproblemen, spierpijn, en vermoeidheid, zou zorgen voor een voortschrijdende achteruitgang in fysieke mobiliteit, en dat hierdoor patiënten ook frequenter zouden vallen.

Uit de studie die beschreven wordt in **hoofdstuk 5**, wordt duidelijk dat de gemiddelde fysieke mobiliteit van PPS-patiënten op de lange termijn in bescheiden mate achteruitgaat. De geobserveerde loopcapaciteit verminderde met 6% en ervaren mobiliteit met 14% gedurende 10 jaar, in het cohort waarbij 15% quadricepskrachtsvermindering werd gevonden (hoofdstuk 2). Deze achteruitgang werd weerspiegeld door een toename van het aantal mensen dat loophulpmiddelen gebruikte en een toename in het gebruik van meer ondersteunende typen hulpmiddelen. De bevinding dat de achteruitgang over het algemeen bescheiden is zou voor de meeste mensen een geruststelling moeten zijn. Niettemin ging een vijfde van de groep in dezelfde periode aanzienlijk achteruit in loopcapaciteit (-27%) en ervaren mobiliteit (-38%). Het verlies van quadricepskracht kon slechts een klein deel van de variantie in de afname van loopcapaciteit verklaren (R=11%) en de snelheid van achteruitgang kon niet worden voorspeld uit patiëntkenmerken aan het begin van de studie. De individuele variabiliteit in combinatie met het ontbreken van voorspellende factoren benadrukt de noodzaak om bij PPS-patiënten zorgvuldig de individuele functionele achteruitgang te monitoren, zo mogelijk met objectieve maten (bijvoorbeeld spierechografie, hoofdstuk 3). Zodoende kan ook de zorg op het individu worden afgestemd, door op basis van daadwerkelijke functionele achteruitgang op maat gemaakte interventies aan te bieden.

In de retrospectieve cohortstudie in **hoofdstuk 6**, werd door middel van vragenlijsten en statusonderzoek onder 305 deelnemers bevestigd dat vallen een belangrijk probleem is voor patiënten met doorgemaakte polio. Valincidenten kwamen veelvuldig voor in deze groep (74% was ≥1 maal gevallen in het afgelopen jaar), gebeurden vaak (60% was ≥2 maal gevallen) en veroorzaakten veel verwondingen (16% van de degenen die waren gevallen had zware

en 64% milde verwondingen). Ook was de angst om te vallen wijd verspreid in dit cohort (63%), waarbij bijna een kwart van de deelnemers (23%) aangaf minder vaak of ver te lopen door deze angst. De angst om te vallen, samen met de quadricepskracht van het zwakste been, en de zelf-gerapporteerde problemen met balanshandhaving waren onafhankelijk geassocieerd met een hogere valincidentie in dit cohort. De meeste mensen rapporteerden dat valincidenten optraden in een bekende omgeving (86%), tijdens het mobiliseren (72%) en in de middag (50%). De grote hoeveelheid valincidenten en de ernst van de gevolgen van het vallen benadrukken de noodzaak voor de implementatie van valinterventiestrategieën. Om een maximaal effect te bereiken zullen deze individueel op maat moeten worden gemaakt en afgestemd moeten worden op de valmechanismen die specifiek zijn voor deze patiënten.

In **hoofdstuk** 7 worden de belangrijkste bevindingen en de methodologische afwegingen van dit proefschrift samengevat en de klinische betekenis daarvan bediscussieerd. Onder andere wordt besproken hoe de resultaten kunnen worden gebruikt om de informatievoorziening aan en begeleiding van patiënten te verbeteren. Ook wordt besproken hoe de bestaande methoden voor monitoring van veranderingen in kracht en fysiek functioneren kunnen worden verbeterd. Tenslotte, worden aanbevelingen voor toekomstig onderzoek gedaan. We stellen voor om onder andere verder onderzoek te doen naar de longitudinale gevoeligheid van spierechografie en naar het ontwikkelen van specifieke valinterventiestrategieën voor postpoliopatiënten. Daarnaast introduceren we het idee om wereldwijde kennisplatforms te initiëren en onderhouden om de huidige kennis over het postpoliosyndroom te delen met de landen die het in de toekomst het meest nodig zullen hebben.



Section E

Appendices

Dankwoord





About the author

Curriculum vitae Publications Portfolio

Curriculum vitae

Alice Bickerstaffe was born on December 6th, 1981 in Hilversum, the Netherlands and is a British citizen. From 1990 to 1996 she attended the Heilig Hart College in Tervuren, Belgium. In 1999 she graduated from secondary school at the Alberdingk Thijm International School in Hilversum. After a gap year in South America and obtaining a propedeuse in Biology at the Radboud University in Nijmegen, she started studying Medicine at the same college. During her medical degree she also achieved an honours degree by completing the Radboud university Honours Programme in 2004. Alice rounded off her medical degree with an internship in Biharamulo District hospital in Tanzania in 2007 and a scientific research project at the department of neurology of the Radboud UMC in 2008. Directly thereafter she worked for one year as a resident in neurology (ANIOS) at the Sint Franciscus Gasthuis in Rotterdam. In 2009 she started working on this PhD at the department of Rehabilitation Medicine of the Academic Medical Center (AMC) in Amsterdam. The PhD measurements were conducted at the AMC and Radboud UMC under supervision of prof. dr. Frans Nollet, dr. Anita Beelen and dr. ing. Hans van Dijk and dr. Machiel Zwarts. Since January 2014 she is a resident of rehabilitation medicine (AIOS) at the AMC and READE, Center for Rehabilitation and Rheumatology, in Amsterdam.

Alice lives in Amsterdam with Jason Levin-Koopman and their son Noah.

Publications

Horlings C, Munneke M, Bickerstaffe A, Laverman L, Allum J, Padberg G, Bloem B, van Engelen B. *Epidemiology and pathophysiology of falls in facioscapulohumeral disease*. J Neurol Neurosurg Psychiatry 2009 Dec;80(12):1357-1363.

Bickerstaffe A, Beelen A, Nollet F. *Circumstances and consequences of falls in polio survivors*. J Rehabil Med 2010 Nov;42(10):908-915.

Bickerstaffe A, van Dijk JP, Beelen A, Zwarts MJ, Nollet F. Loss of motor unit size and quadriceps strength over 10 years in post-polio syndrome. Clin Neurophysiol 2014 Jun; 125(6):1255-1260.

Bickerstaffe A, Beelen A, Zwarts MJ, Nollet F, van Dijk JP. *Quantitative muscle ultrasound and quadriceps strength in patients with post-polio syndrome*. Muscle Nerve 2015 Jan;51(1):24-29.

Bickerstaffe A, Beelen A, Nollet F. *Change in physical mobility over 10 years in post-polio syndrome*. Neuromuscul Disord 2015 Mar;25(3):225-230.

Bickerstaffe A, Beelen A, Lutter R, Nollet F. *Elevated plasma inflammatory mediators in post-polio syndrome: No association with long-term functional decline*. J Neuroimmunol 2015 Dec 15;289:162-167.

Portfolio

Name PhD student:	Alice Bickerstaffe
PhD period:	September 2009 – April 2016
Name PhD supervisor:	Prof. dr. F. Nollet

1. PhD training

	Year	Workload (hours/ECTS)
General courses		
Practical biostatistics, AMC graduate school, Amsterdam	2010	40/1.4
Pubmed, AMC graduate school, Amsterdam	2010	4/0.1
Basic course in legislation and organization for clinical researchers (BROK), AMC graduate school, Amsterdam	2012	28/1
Advanced topics in biostatistics, AMC graduate school, Amsterdam	2014	60/2.1
BROK refresher, VU, Amsterdam	2016	4/0.1
Specific courses		
PhD-school: Outcome measures in Rehabilitation Research, University of Southern Denmark, Copenhagen, Denmark	2009	32/1.1
EMG, VU faculty of Human Movement Sciences, Amsterdam	2010	84/3
Rehabilitation: restoration of mobility, VU faculty of Human Movement Sciences, Amsterdam	2011	84/3
Clinical movement analysis, VU faculty of Human Movement Sciences, Amsterdam	2011	84/3
Fall prevention and fall training, St. Maartenskliniek, Nijmegen	2012	28/1
Muscle and nerve ultrasound, UMC St. Radboud, Nijmegen	2012	14/0.5
Presentations		
Yearly department presentations, AMC, Amsterdam, the Netherlands [orals]	2009-2014	84/3
Changes in muscle strength and motor units in 10 years in a homogenous cohort with symptomatic quadriceps muscles. PhD- school Denmark, Copenhagen, Denmark [poster]	2009	14/0.5
Falls in polio survivors: research plan. Symposium for visiting prof. dr. K. Borg, Sweden in honour of the PhD defense of J. Stolwijk-Swüste, AMC, Amsterdam, the Netherlands	2009	14/0.5
The frequency, consequences and aetiology of falls in polio survivors. 1 st Baltic and North Sea Conference on PRM, Stockholm, Sweden [oral]	2010	14/0.5
Falls in polio survivors. 1 st symposium Verstoord Bewegen, AMC, Amsterdam, the Netherlands [oral]	2011	14/0.5
Circumstances and consequences of falls in Post Polio Survivors. 16 th WCPT congress, Amsterdam, the Netherlands [poster]	2011	14/0.5
The frequency, consequences and aetiology of falls in polio survivors. PHI, international telephone conference [oral]	2011	14/0.5

	Year	Workload (hours/ECTS)
Falls in polio survivors, for professionals, 1 st European polio conference, August 31-September 2, Copenhagen, Denmark [oral]	2011	14/0.5
Falls in polio survivors, for patients, 1 st European polio conference, August 31-September 2, Copenhagen, Denmark [oral]	2011	14/0.5
Omstandigheden en gevolgen van vallen na doorgemaakte polio. Spierziektecongres, VSN, Veldhoven, the Netherlands [poster]	2012	14/0.5
Reduction in size of enlarged motor units and concomitant loss of quadriceps strength over 10 years in Post-polio patients. Refereeravond revalidatieartsen, AMC, Amsterdam, the Netherlands [oral]	2013	14/0.5
Reduction in size of enlarged motor units and concomitant loss of quadriceps strength over 10 years in Post-polio patients, 7 th ISPRM World Congress, Beijing, China [oral]	2013	14/0.5
Changes in muscle strength and MU-size in PPS. Neuroteam, AMC, Amsterdam, the Netherlands [oral]	2013	14/0.5
PhD overview: Muscular changes and functional problems in PPS. Slotervaart, Amsterdam, the Netherlands [oral]	2014	14/0.5
Changes in muscle strength and motor units in patients with post- poliomyelitis syndrome (PPS). ESPRM, June, Marseille, France [oral]	2014	14/0.5
Quantitative muscle ultrasound and quadriceps strength in patients with post-polio syndrome. ESPRM, June, Marseille, France [oral]	2014	14/0.5
Cytokine levels and association with physical decline over 10 years in post-polio syndrome. 2 nd European polio conference, June 25-27, Amsterdam, the Netherlands [poster]	2014	14/0.5
Quantitative muscle ultrasound and quadriceps strength in patients with post-polio syndrome. 2 nd European polio conference, June 25-27, Amsterdam, the Netherlands [oral]	2014	14/0.5
Attended seminars, symposia		
Symposium for visiting prof. dr. K. Borg, Sweden in honour of the PhD defense of J. Stolwijk-Swüste, AMC, Amsterdam	2009	4/0.1
Graduate school inspirational evening seminar 'Scientists come out of your lab', Amsterdam	2010	4/0.1
1st symposium Verstoord Bewegen, November, AMC, Amsterdam	2011	4/0.1
Symposium, 'zorg voor zelfstandigheid', prinses Beatrix fonds, September 30, Utrecht	2011	4/0.1
De anatomische les, November 3, Amsterdam	2011	4/0.1
Graduate school inspirational evening seminar 'Insane in the brain', Amsterdam	2011	4/0.1
2 nd symposium Verstoord Bewegen, April 24, AMC, Amsterdam	2012	4/0.1
De anatomische les, November, Amsterdam	2012	4/0.1
3 rd symposium Verstoord Bewegen, November 22, AMC, Amsterdam	2013	4/0.1

		Workload
	Year	(hours/ECTS)
Attended (Inter)national conferences		
1 st Baltic and North Sea Conference on PRM, April 14-16, Stockholm, Sweden	2010	24/0.9
16 th WCPT congress, June 20-23, Amsterdam, the Netherlands	2011	4/0.1
1 st European polio conference, August 31-September 2, Copenhagen, Denmark	2011	24/0.9
Spierziektecongres, VSN, september 15, Veldhoven, the Netherlands	2012	8/0.3
7 th International Society of Physical and Rehabilitation Medicine (ISPRM) World Congress, June 16-20, Beijing, China	2013	32/1.1
19 th European congress of physical and rehabilitation medicine (ESPRM), May 26-31, 2014, Marseille, France	2014	16/0.6
2 nd European polio conference, June 25-27, Amsterdam, the Netherlands	2014	24/0.9
Dutch Congress of Rehabilitation Medicine, VRA colloquiem, April, Zwolle, the Netherlands	2014	8/0.3
Dutch Congress of Rehabilitation Medicine, VRA colloquiem, April, Amsterdam, the Netherlands	2015	8/0.3
Dutch Congress of Rehabilitation Medicine, VRA, November, Rotterdam, the Netherlands	2015	24/0.9
Dutch Congress of Rehabilitation Medicine, VRA colloquiem, April, Amsterdam, the Netherlands	2016	8/0.3
Other		
Board member organising 1 st symposium 'verstoord bewegen', a cross- disciplinary symposium for AMC PhD-students	2011	28/1
Board member organising junior researcher meetings department rehabilitation AMC	2013	28/1

2. Teaching

	Year	Workload (hours/ECTS)
Workshop 'met vallen en opstaan' (falls in PPS), with occupational therapist D. Toor and physical therapist T. Sassen, Spierziektecongres, VSN, Oktober 9, Veldhoven, the Netherlands	2011	20/0.7
Workshop 'met vallen en opstaan' (falls in PPS), Spierziektecongres, VSN, September 15, Veldhoven, the Netherlands	2012	20/0.7
Supervising/mentoring student research assistant. Title: activity monitoring in PPS-patients.	2012-2013	28/1

3. Parameters of esteem

	Year	
Best poster award. Cytokine levels and association with physical decline over 10 years in post-polio syndrome. 2 nd European polio conference, June 25-27, Amsterdam, the	2014	
Netherlands		

Stellingen

behorende bij het proefschrift

Pathophysiology of muscular changes in post-polio syndrome and consequences for physical mobility

- 1. Size diminution of enlarged MUs combined with a reduced number of active MUs contributes to the gradual strength decline in PPS. *(This thesis)*
- 2. Muscle ultrasound distinguishes diseased from healthy muscles by measurement of muscle quantity and quality. (*This thesis*)
- 3. Muscle ultrasound is a promising diagnostic tool for assessing clinical disease severity in PPS patients, particularly those who have complaints that limit strength testing. *(This thesis)*
- 4. There is a systemic inflammation in PPS and indications that monocytic TNF-α drives these responses, yet no apparent relationship with clinical deterioration. (*This thesis*)
- 5. The remaining muscle tissue of PPS-patients can best be compared to that of master athletes, and is maintained at an optimum through 'training' during every day activities. (*This thesis*)
- 6. The individual variability in rate of decline in mobility, yet lack of predictive factors, underscores the need for personally tailored care based on actual functional decline in patients with post-polio syndrome (*This thesis*)
- 7. The high rate of falls and consequences thereof, merit the implementation of fall intervention strategies. To maximize effect, they should be tailor-made and target the fall mechanisms specific to polio survivors. (*This thesis*)
- 8. Life is far too important to be taken seriously. (Oscar Wilde)
- 9. It always seems impossible until it's done. (Nelson Mandela)
- 10. Here I am, where I ought to be. (Karen Blixen)