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POST-POLIO SYNDROME – PHYSIOTHERAPEUTIC ANALYSIS AND INTERVENTIONS

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To my family.

ABSTRACT

This thesis presents four studies focusing on outcomes of gait performance using gait analysis and/or the Six-minute-walk test (6MWT), in patients with post-polio syndrome (PPS). Further, resistance training in combination with Coenzyme Q10 (Q10) and intravenous immunoglobulin treatment (IvIg) in PPS patients was evaluated.

Study I was a test-retest reliability study where 23 PPS patients completed three 6MWT. Results of the study pointed to increased fatigue in later tests among patients who walked with walking aids. The intra-class correlation coefficient ($ICC_{2.1}$) values were high indicating high reliability. The standard error of measurement (SEM) and the smallest real difference (SRD) were reasonably small implying that the 6MWT has acceptable sensitivity and can be used to detect real clinical changes in a group as well as in a single individual.

Study II aimed to investigate, with gait analysis, that is, 3-dimensional (3D) movement analysis during a clinical 6MWT, gait variables and the influence of fatigue, in 18 PPS patients compared to 11 healthy controls. The results indicated fatigability in the PPS group compared to the controls. A distinct plantar-flexed ankle at initial contact (IC) was seen in the PPS patients. However, the most striking finding of the study was related to the hip joint which, at foot-off (FO), was flexed in the patients while extended in the controls. The increased hip flexion at FO was negatively correlated with walking speed.

Study III was a randomized placebo-controlled study, evaluating the effect of resistance training combined with oral supplementation with Q10 in 14 patients with PPS. The result confirmed that muscle training leads to increased muscle strength, muscle endurance and mental health. There were, however, no statistically significant differences between the Q10 group and the placebo group for any of the evaluations.

Study IV evaluated the effects of treatment with IvIg on primarily gait ability, measured with 3D gait analysis, in 17 PPS patients. A sub-group performed a 12-week muscular resistance training programme. Walking distance and isometric knee flexion strength increased while hip- and knee flexion at FO decreased after the 12 weeks for all participants. IvIg, in combination with training, resulted in a further increase in walking distance as well as improved general health and less general fatigue.

In conclusion, the 6MWT is a reliable test for evaluating gait ability in PPS patients. One test may be enough for clinical purposes, but the best results of two tests can be used for research purposes. Compared to healthy controls, PPS patients walked with plantar-flexed ankle at IC and an increased hip flexion at FO. The latter negatively correlated with walking speed. Muscle training had positive effects in PPS patients regarding walking distance as well as muscle strength and mental health, with no added benefit from supplementation with Q10. Treatment with IvIg resulted in increased walking distances and isometric knee flexion strength as well as a decreased hip- and knee flexion at FO. An additional training programme had some further positive effects. However, whether muscle training enhances the effect of IvIg cannot be fully answered on the basis of the present data**.**

Keywords: Post-polio syndrome, Six minute walk test, Gait analysis

SAMMANFATTNING PÅ SVENSKA

Avhandlingen består av fyra studier som fokuserar på gångförmåga utvärderat med gånganalys och/eller sex minuters gångtest (6MWT), hos patienter med post-polio syndromet (PPS). Vidare har styrketräning i kombination med koenzym Q10 (Q10) och behandling med intravenöst immunglobulin (IvIg) hos patienter med PPS utvärderats.

Studie I var en test-retest reliabilitetsstudie där 23 patienter med PPS utförde tre 6MWT. Resultaten av studien pekade på en ökning av trötthet i senare tester för patienter som gick med hjälp av gånghjälpmedel. Intraklass korrelations koefficienten ($ICC_{2.1}$) visade höga värden vilket indikerar en hög reliabilitet. Standard error of measurement (SEM) och smallest real difference (SRD) visade relativt låga värden vilket tyder på att 6MWT har en acceptabel känslighet och därmed kan användas för att upptäcka kliniska förändringar i en grupp såväl som hos en enskild individ.

Studie II syftade till att med gånganalys, dvs 3-dimensionell (3D) rörelseanalys under ett kliniskt 6MWT, undersöka gångvariabler och påverkan av trötthet hos 18 patienter med PPS jämfört med 11 friska kontroller. Resultaten av studien pekade på trötthet under testet hos patientgruppen jämfört med de friska kontrollerna. En distinkt plantarflekterad fotled vid fotisättningen (Initial Contact, IC) sågs hos patienterna. Det mest slående fyndet i studien avsåg emellertid höftleden, då höften vid fotavvecklingen (Foot Off, FO) var flekterad hos patienterna och extenderad hos kontrollerna. Den ökade höftflexionen vid FO var negativt korrelerad med gånghastighet.

Studie III var en randomiserad, placebokontrollerad studie där effekten av styrketräning i kombination med tillskott av Q10, hos 14 patienter med PPS, utvärderades. Resultatet av studien bekräftar att muskelträning har positiva effekter, i aktuell studie gällande muskelstyrka, uthållighet och mental hälsa. Det fanns dock inga statistiskt signifikanta skillnader mellan Q10- och placebogruppen.

Studie IV syftade till att utvärdera effekten av behandling med IvIg gällande främst gångförmåga, mätt med registrering av rörelseanalys i 3D under ett kliniskt 6MWT hos 17 patienter med PPS. En undergrupp utförde ett 12-veckors styrketräningsprogram. För totala antalet deltagare ökade gångsträcka och isometrisk knästyrka medans höft- och knä flexion vid FO minskade efter 12 veckor. IvIg i kombination med träning resulterade i en ytterligare ökning av gångsträcka samt förbättrad generell hälsa och minskad generell trötthet.

Sammanfattningsvis, 6MWT är ett reliabelt test för utvärdering av gångförmåga hos patienter med PPS. Ett test kan vara tillräckligt för klinisk praxis, men det bästa resultatet av två tester kan användas inom forskning. Jämfört med friska kontroller, går patienter med PPS med planktarflekterad fotled vid IC och med en ökad höftflexion vid FO. Den sistnämnda var negativt korrelerad med gånghastigheten. Muskelträning visade på positiva effekter hos patienter med PPS med ökad gångsträcka, muskelstyrka och mental hälsa, utan ytterligare gynnsam effekt av kosttillskott med Q10. Behandling med IvIg resulterade i ökad gångsträcka och isometrisk muskelstyrka i knäflexion samt minskad höft- och knä flexion vid FO. Träning resulterade i viss ytterligare effekt, men om muskelträning förbättrar effekten av IvIg kan dock inte helt besvaras utifrån aktuell studie.

LIST OF PUBLICATIONS

The thesis is based on the following papers, which are referred to in the text by their Roman numerals (I-IV).

I. K. Skough, L. Broman, K. Borg
Test-retest reliability of the six minute walk test in subjects with post-polio syndrome.
Accepted for publication in International Journal of Rehabilitation and Research, 2012-10-02

II. K. Skough, J. Henriksson, K. Borg, M. Henriksson
Gait characteristics and influence of fatigue during 6-Minute Walk Test in patients with post-polio syndrome – a pilot study.
Submitted to Journal of Rehabilitation Medicine, 2012-12-14

III. K. Skough, C. Krossén, S. Heiwe, H. Theorell, K. Borg
Effects of resistance training in combination with coenzyme Q10 supplementation in patients with post-polio: a pilot study.
Journal of Rehabilitation Medicine 2008; 40: 773-775

IV. K. Skough, M. Henriksson, J. Henriksson, K. Borg
Effects of IvIg treatment on gait in patients with post-polio syndrome – a pilot study.
Manuscript

CONTENTS

List of abbreviations

ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
CR	Category ratio
EMG	Electromyography
FO	Foot-off
FTSST	Five-times-sit-stand-sit test
IC	Initial contact
ICC	Intra-class correlation coefficient
ICF	International Classification of Functioning, Disability and Health
IvIg	Intravenous immunoglobulin treatment
J	Joule
KAFO	Knee-ankle-foot orthoses
KinCom	Kinetic communicator
MFI	Multidimensional Fatigue Inventory
MMT	Manual muscle testing
MWT	Minute-walk-test
PASE	Physical Activity Scale for the Elderly
Polio	Poliomyelitis
PPS	Post-polio syndrome
Q10	Coenzyme Q10
RCT	Randomized controlled trial
RM	Repetition maximum
ROM	Range of motion
RPE	Ratio of perceived exertion
RTP	Rehabilitering, tillgänglighet och påverkan (Rehabilitation, accessibility and influence)
SD	Standard deviation
SEM	Standard error of measurement
SF-36	Short form-36
SIP	Sickness impact profile
SRD	Smallest real difference
SSS	Sit-stand-sit test
TUG	Timed-up-and-go
UNICEF	United Nations Children’s Fund
VAS	Visual analoge scale
WHO	World Health Organization
3D	Three-dimensional

1 INTRODUCTION

1.1 POLIOMYELITIS (POLIO)

The word poliomyelitis comes from the Greek *polios* = grey, *myelos* = marrow and *-itis* = inflammation. Poliomyelitis, or polio, is caused by a virus. There are three types of wild polio virus, type 1, type 2 and type 3. Polio mainly affects children under the age of five years, but can strike at any age [1]. The virus enters the body through an oral pathway, through contaminated food and water, and multiplies in the intestine. Many people infected by polio have no symptoms, but excrete the virus in their faeces, hence transmitting the infection to others. Polio virus initially causes influenza symptoms such as fever, fatigue, headache, vomiting, stiffness in the neck and pain in the limbs. In some, but not in all, cases the polio virus gives a paralysis [1-2]. The earlier in life you are infected, the less the risk of paralysis and permanent disability [3].

Polio was brought under control in the industrialized countries after introduction of vaccines in the 1950s and 1960s. In the1970s it became known that the polio virus was also prevalent in developing countries, and routine immunization was introduced worldwide. The Global Polio Eradication Initiative began in 1988 with the goal to eradicate polio worldwide [1]. It is a public-private partnership led by national governments and spearheaded by partners, among them the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF).

Today polio remains endemic in Afghanistan, Nigeria and Pakistan. Polio virus type 2 was most recently detected in India in 1999 and types 1 and 3 continue to circulate in endemic areas [1].

Currently 12-20 million world-wide have sequelae of poliomyelitis, according to Post-polio Health International. The number of polio patients in the Swedish population is estimated to be 15 000-20 000 [4].

1.1.1 Paralysis as a result of polio virus

The polio virus affects the anterior horn cells of the spinal cord, leading to a flaccid and asymmetric paralysis. After the acute infection, a clinical improvement is often seen, where the paralysis can decrease or even disappear completely. This is mainly due to reinnervation, "sprouting". "Sprouting" is an effective process of the motor units, where intact neurons grab muscle fibres without nerve contact [2, 5], see figure 1. A stable period follows with an ongoing denervation-reinnervation process [6].

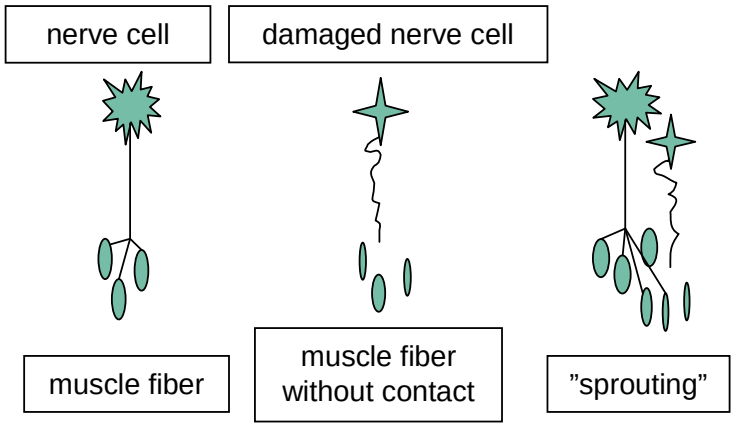

Figure 1. Polio virus destroys the nerves to the muscles, and the nerves are repaired by “sprouting”, the “denervation-reinnervation process”.

Infection resulting in paralysis most often affects the legs. Paralysis can, however, also involve the trunk, arms and respiratory muscles reducing breathing capacity. When the brain stem is affected, polio can cause difficulty in swallowing and speaking, bulbar polio [1].

1.1.2 Post-polio syndrome (PPS)

Many patients with prior polio risk developing new or increased symptoms, and this is termed the post-polio syndrome (PPS). The PPS appears usually at least 15 years after the acute polio [7]. Besides increased muscle weakness, the PPS comprises symptoms such as fatigue, muscle- and joint pain (see schedule below) [5, 7].

Different criteria for PPS have been proposed and used by different polio clinics [8]. However, there is today a consensus to use the March of Dimes criteria [7]. Diagnosis is based on medical history, typical findings on physical examination and neurophysiological study (electromyography (EMG)), see schedule below.

Criteria for PPS, given by March of Dimes:

1. Prior paralytic poliomyelitis with evidence of motor neuron loss
2. A period of partial and complete functional recovery after acute paralytic poliomyelitis followed by a period of stable neurological function
3. Gradual or sudden onset of progressive and persistent new muscle weakness or abnormal muscle fatigability, with or without generalized fatigue, muscle atrophy or muscle and joint pain
4. Symptoms persisting for at least a year and
5. Exclusion of other neurological, medical and orthopaedic problems as cause of symptoms.

The prevalence of PPS is reportedly between 20% and 85% [5]. An exact value may be difficult to establish due to the use of different clinical diagnostic criteria. Although the number of polio patients will decrease in the western world during the next few decades, it will remain high in developing countries for the coming generation. Native Swedish patients at the post-polio outpatient clinics are today about 55 years of age and older. However, an increased number at the Swedish clinics are immigrants and younger. PPS will therefore be of interest in Swedish health care for many years to come.

The most common complaints among PPS patients muscle weakness, fatigue, pain and limitations in walking, are all included in the WHO International Classification of Functioning, Disability and Health (ICF) dimension Functioning and Disability. Muscle weakness, fatigue and pain, are included in the Body Functions and Structures part while walking is included in the Activities and Participation part.

Limitations in walking are one of the most prominent problems described by this patient group [9] and reduced gait velocity has been recorded [10]. Weakness in lower-limb muscles affects gait. A non-linear association between muscle strength and activity limitations in patients with neuromuscular disorders has been shown by Vandervelde et al [11], due to compensatory neuromuscular mechanisms. Lower-limb weakness in polio patients is, however, directly associated with falls [12-13], and with increased sway [12]. Prior polio patient also has reduced balance compared to healthy persons [10]. Braces are intended to improve mobility and reduce pain and overuse of muscles and joints and are commonly used by patients with prior polio. Ongoing technical developments of orthopaedic braces, including lightweight and strong materials, make them more appealing and useful for patients to wear. Use of lightweight braces by polio patients can save energy while walking. This was shown by Brehm et al [14] who compared a total-contact fitted carbon-composite knee-ankle-foot-orthoses (KAFO) with a conventional leather/metal KAFO for polio patients. The energy cost decreased significantly when using the carbon-composite KAFO [14].

Fatigue in patients with PPS is multidimensional [15]. Östlund et al [16] showed that fatigue in PPS was mainly physiological. However, a sub-group of younger patients with a shorter polio duration, more pain, higher body mass index (BMI) and lower quality of life had both physical and mental fatigue [17].

Pain is another common symptom [18-19]. A study by Willen and Grimby [19] found that more than half of patients with prior polio and PPS experienced pain daily with a mean Visual Analogue Scale (VAS) score of 55. In another study, pain was present in two thirds of PPS patients. Almost all pain was of nociceptive character and of relatively high intensity. Pain was more frequently reported by women than by men, and more often in younger patients [18].

There is now a consensus regarding the background of PPS, see chapter 1.2 below.

No specific treatment, only symptomatic treatment is used today for PPS patients. Physiotherapy seeking to increase or maintain motor function is often recommended. Of great importance is also information and education in PPS, life-style changes including activity modification with more frequent rest breaks, and technical aids,

walking aids and orthoses for relief of weak muscles and joints. With the high number of patients with sequelae of polio further scientific studies to increase or maintain muscle function and quality of life are of great importance.

1.2 THE MOTOR UNIT AND POLIO

The peripheral nervous system consists of the motor unit, i.e. the motor neuron and its muscle fibres. Motor units with lower axonal conduction velocity are recruited before units with higher. The motor unit consists of different muscle fibres, subdivided into type I (slow twitch) and type II (fast twitch). Motor neurons with the lowest thresholds innervate type I muscle fibres, which contract and relax slowly and are fatigue-resistant, while motor neurons with the highest threshold innervate type II fibers, which contract fast and are easily fatigued. There is a relatively uniform mixture of fast and slow fibres in the muscles, although, some variation in proportions of fast and slow fibres are seen between different muscles, depending on their function [20], and also between individuals.

Several compensatory phenomena take place in PPS motor units, as seen in table 1. Several studies have shown an increase in muscle fibre area in subjects with prior polio [6, 21-26]. The large muscle fibre areas may due to overuse of the remaining muscle fibres in patients with PPS with low muscle strength.

Despite the increased muscle fiber area the number of capillaries in contact with type I fibers is significantly lower in patients than in controls [22] and Grimby et al [6] showed a decrease in capillarization, in polio patients, during an eight-year follow up. This might be an explaination for the fatigue and muscle pain experienced by patients with PPS.

An increase in type I (slow-twitch) muscle fibres has been described in prior polio patients [22, 27] and may be due to a transition of type II to type I. This was shown, by Borg et al, to be supported by the finding of type I fibres containing both slow and fast myosin [27] as well as no loss of type II motor units [28].

There are also differences in motor unit recruitment. Residual muscle fibres in prior polio patients with overuse are largely used in an all-or-none manner. Changes in the contractile properties of the remaining muscle fibres, in the tibialis anterior muscle, favour muscle strength before endurance [29]. Einarsson [23-24] has shown low oxidative enzyme activity in post-polio muscles. These may be factors causing the muscle fatigue in PPS patients.

The most powerful compensatory phenomenon in PPS is reinnervation. The ongoing denervation-reinnervation process in patients with PPS (see chapter 1.1.1 above) results in larger motor units, making it possible for fewer motor neurons to do the work of many. An approximate breakpoint for motor-unit size seems to be around 20 times the normal size as described by Grimby et al [6]. When motor-unit size has reached an

upper limit, further losses of neurons can no longer be compensated for. This results in uncompensated denervation and, thereby, increased muscle weakness [6].

Table 1.
Compensatory muscle phenomena in patients with PPS.

Compensatory muscle phenomena in PPS	References
Muscle fibre hypertrophy	Grimby et al [6, 25-26], Borg et al [21-22] Einarsson [23-24]
Capillarization	Borg, Henriksson [22], Grimby et al [6]
Increase in type I muscle fibre	Borg, Henriksson [22], Borg et al [27]
Muscle fibre transition	Borg et al [27]
Alterations in motor unit recruitment	Larsson et al [29]
Oxidative enzyme activity	Einarsson [23-24]

1.3 MUSCLE TRAINING AND POLIO

Physical activity is an important component of everyday living, with many beneficial changes both physiologically and psychologically. With prolonged muscle training, the muscle fibres normally react by adaptation to a higher level of performance. Normally an improved cardiovascular conditioning and neural activation is seen during the first 6-8 weeks of muscular training and, thereafter, an increase of muscle volume and strength can be seen. Fibre size increases as a result of endurance training, mainly in type I muscle fibres. In healthy individuals, high-resistance training gives an increase in muscle volume and strength corresponding to a larger cross-sectional area of muscle fibres [30]. Muscle fibre hypertrophy after heavy resistance training has been reported to occur mainly in type II muscle fibres [30-31].

In patients with PPS, few randomised controlled trials have investigated the effect of muscle training. Two randomised controlled trials have shown positive effects of muscle training and aerobic exercise programme respectively [32-33]. However, several non-randomised controlled trials have shown that muscle resistance training in post-polio patients increases muscle strength and/or performance [8, 23-24, 34-38]. Patients reporting regular physical activity have shown less muscle pain and fatigue than physically inactive patients [39]. The benefits of exercise in patients with PPS appear to occur when the patients exercise at a reasonable level, avoiding overuse problems. In particular, it is important to instruct patients to avoid activities that cause increasing muscle or joint pain, as well as excessive fatigue, during or after an exercise programme [40-41]. Whether the reinnervation-process is beneficially affected by physical activity has not been established [41]. A study evaluating cardio-respiratory response after a 16-week aerobic exercise programme showed that patients with PPS respond to training in a manner similar to healthy persons. The exercise was performed on a cycle ergometer, at 70% of maximal heart rate [33]. A training programme

focusing on endurance and performed by patients with PPS over six months showed an increase in muscle strength in some muscle groups, as well as in work performance with respect to heart rate at sub-maximal work load, [35]. Willén et al showed that dynamic exercise in warm water decreased heart rate, reduced pain and led to a subjective positive experience [42] and had positive effects on self-confidence [43].

Based on the findings from earlier training studies, some of them outlined above, it was suggested that PPS patients with near-normal muscle strength and no signs of motor-unit reinnervation can be recommended heavy resistance training. Patients with moderate paresis and signs of reinnervation can be recommended sub-maximal endurance training while those with severe paresis should avoid muscle training [44-45]. However, the initial poliomyelitis affected each patient differently, resulting in differing pattern of muscle weakness in each patient. The weakness is often asymmetrical, which may lead to both over- and low use in the same patient. It is therefore of great importance that the training programme be individually planned and supervised by a trained physiotherapist [19, 41, 46], and the training should be differentiated for different muscles, when necessary, and carefully followed up. Patients with PPS should also especially avoid overexertion [41]. For these patients, as well as for healthy subjects, it is very important to find suitable physical activity for cardiovascular conditioning.

1.4 PHARMACOLOGICAL INTERVENTIONS

A few studies of pharmacological treatment for patients with PPS exist (table 2). Prednisone in high-doses has only shown a modest trend to increase muscle strength in patients with PPS and was not recommended as treatment for this patient group [47]. While Lamotrogine has shown positive effects on pain, fatigue and health-related quality of life [48]. In a study by Stein et al [49], Amantadine decreased fatigue in PPS patients. However, a similar decrease was seen also in the placebo group. Horemans et al [50] found a slight effect of Pyridostigmine on physical performance, but a study by Trojan et al [51] showed no differences between pyridostigmine and placebo treated PPS patients. Modafinil has shown some success in reducing fatigue in patients with other neurological conditions such as narcolepsy [52] and myotonic dystrophy [53]. Although PPS patients' complain of fatigue, Modafinil has proved ineffective [54]. For results of pharmacological treatment with Coenzyme Q10 (Q-10) and intravenous immunoglobulin treatment (IvIg), see section 3.3.1 and 3.3.2 below.

Table 2. Medical interventions used in patients with PPS.

Medical Interventions	References
Prednisone	Dinsmore et al [47]
Lamotrogine	On et al [48]
Amantadine	Stein et al [49]
Pyridostigmine	Horemans et al [50], Trojan et al [51]
Modafinil	Vasconcelos et al [54], Chan et al [55]
Coenzyme Q10	Mizuno et al [56] + (III)
IvIg	Farbu et al, Gonzalez et al, Kaponides et al, [57-60] Östlund et al [61], Werhagen and Borg [62] + (IV)

1.5 EVALUATION INSTRUMENTS AND RATING SCALES

For evaluation instruments and rating scales used in the present thesis, see table 3. Most of these instruments were chosen for the present work since they are frequently used in other studies including those of PPS patients (table 3). For further information about physiotherapy evaluation instruments and rating scales see sections 3.4 and 3.5 below.

Table 3. Evaluation instruments and rating scales used in the present thesis and in other studies including patients with PPS.

Outcomes	References	Present studies
6MWT	[58-60, 63-66]	I-IV
Gait analysis (3D)	[67-69]	II, IV
Isokinetic dynamometer	[24, 66, 70-76]	III, IV
SSS		III
TUG	[10, 59, 64, 66, 77]	III, IV
Borg (RPE, CR-10)	[34, 37, 42]	I-IV
SF-36	[46, 59-61, 63, 77-78]	III, IV
PASE	[19, 59, 61]	IV
MFI-20	[15, 17], [46, 59]	IV
EQ5D		IV
VAS (pain)	[18-19, 59, 61, 79]	IV

2. AIMS

The general aim of the work presented in this thesis was to evaluate the outcome of gait performance and capacity using gait analysis and the Six-minute-walk test (6MWT), respectively, in PPS patients. Further, resistance training in combination with Q10 and IvIg was evaluated with analysis of motor function, including gait characteristics and 6MWT walking distance as well as health-related quality of life.

2.1 SPECIFIC AIMS

Study I
Study I sought to describe the test-retest reliability of the 6MWT in PPS patients. Differences between patients with walking aids and those without were also evaluated.

Study II
The aim of study II was to investigate, with 3-dimensional (3D) movement analysis during a clinical 6MWT, gait variables and the influence of fatigue, in PPS patients compared to healthy controls.

Study III
Study III aimed to evaluate the effect of resistance training combined with oral supplementation with Q10 in patients with PPS regarding muscle strength, functional mobility, muscle endurance and health-related quality of life.

Study IV
Study IV evaluated the effects of treatment with IvIg on gait ability, measured with 3D movement analysis, on PPS patients. A sub-group performed a 12-week muscular resistance training programme. Muscle strength, muscle endurance, functional mobility, health-related quality of life and pain were also evaluated.

3. MATERIAL AND METHODS

3.1 STUDY POPULATION

For participants' recruitment, see figure 2. Patients included in the studies were recruited from the post-polio out-patient clinic at the Department of Rehabilitation Medicine at Danderyd University Hospital. In Study III patients were also recruited from a physical training group for PPS patients, at Danderyd University Hospital, arranged by the patient organisation, Personskadeförbundet RTP -Rehabilitering, Tillgänglighet och Påverkan (Personal Injury Association, Rehabilitation, Accessibility and Influence). The healthy controls, included in Study II, were recruited externally. All patients included had a clinically and neurophysiologically verified diagnosis of PPS, according to the criteria given by March of Dimes [7]. Inclusion criteria for participating in the studies were that the patients were able to walk for six minutes; for the controls that they were healthy and without pain. For characteristics of participants, see table 4.

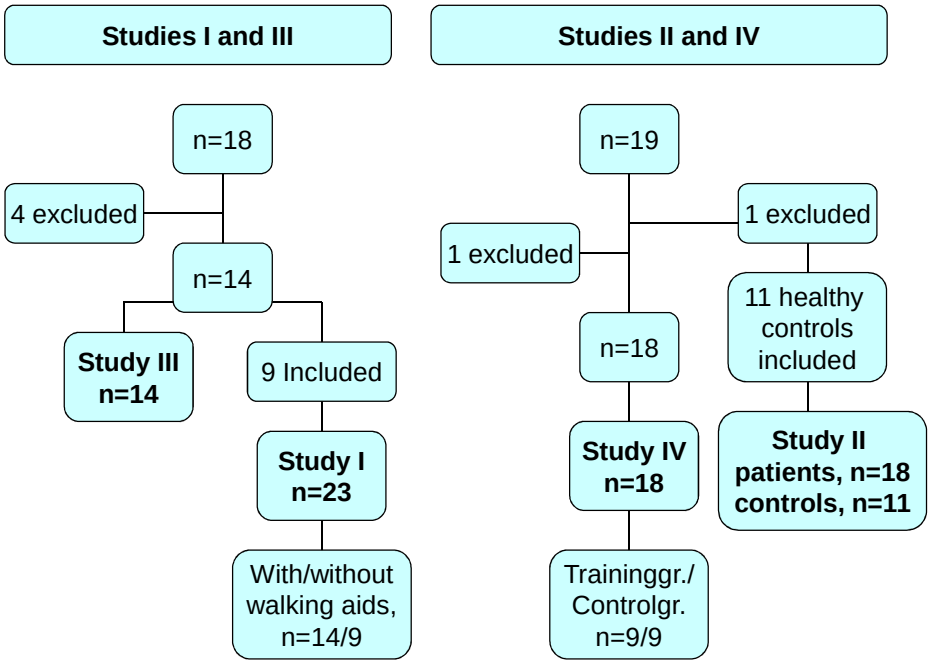

Figure 2. Participants recruitment to Studies I and III (left), and Studies II and IV (right).

Table 4. Characteristics of the patients and healthy controls.

Study	No of subjects	Status	Gender m/f	Age mean ± SD	Polio duration mean ± SD
I	23	patients	9/14	67 ± 7	62 ± 5
II	18	patients	9/9	67 ± 10	59 ± 6
	11	controls	5/6	68 ± 6	
III	14	patients	8/6	69 ± 6	62 ± 5
IV	18	patients	9/9	68 ± 9	61 ± 6

3.2 PHYSIOTHERAPY INTERVENTIONS

3.2.1 Muscle resistance training (III, IV)

The muscle resistance training programmes used in the studies were performed over 12 weeks, three sessions per week with a duration of 30-60 minutes per session. The training was supervised by a physiotherapist (the author, KS). The patients were instructed to avoid excessive fatigue and muscle and joint pain during and after the exercise programme.

The sessions started with a ten minute warm-up on a cycle ergometer, with an intensity corresponding to 10–11 on the Borg Ratio of Perceived Exertion (RPE) scale [80]. The patients then performed muscle resistance training focusing on the lower extremities. For variation, training of the upper extremities was also included, although without evaluation of muscle strength or function. The initial workload was 50–60% of one repetition maximum (1RM) and was successively increased to an intensity of 70–80% of 1RM. The training programmes consisted of cable rear pull-downs, leg presses, arm presses and thoracic/lumbar rotation (all in a sitting position, two sets of 10 repetitions/exercise). In addition, toe heaves were performed standing on a surface at an angle of 10 degrees (one set, maximum number of repetitions/leg). In Study IV, hip abduction, when lying on the side, (two sets of 10 repetitions) and heel rises when standing on a flat floor (one set, maximum number of repetitions/leg) were added to the programme.

3.3 MEDICAL INTERVENTIONS

3.3.1 Coenzyme Q10

Coenzyme Q10 (Q10) is an indispensable compound of the respiratory chain in the inner mitochondrial membrane [81]. In a small study Mizuno et al [56] studied the effect of Q10 in PPS and found an increased muscle energy metabolism. Mizuno´s study, however, contained only a few patients, but nonetheless many PPS patients take Q10 in order to increase muscle strength and function.

Before the start of study III, it was known that many patients with PPS, visiting the post-polio outpatient clinic in Stockholm, took supplementation with Q10. With that knowledge and results of the study by Mizuno et al [56], it was important to perform additional research in the area.

3.3.2 Intravenous immunoglobulin treatment (IvIg)

Studies of cytokines and a proteomic study have indicated an intrathecal inflammatory process in the central nervous system in PPS patients [82-83] and in peripheral blood [58, 84]. The inflammation was down modulated by IvIg [85], which in a randomized clinical trial (RCT) led to increased muscle strength and physical activity and also increased quality of life regarding vitality [59]. Increased quality of life, particularly regarding vitality, after treatment with IvIg, was also found by Kaponides et al [60]. Treatment with IvIg also decreases pain in PPS patients [57, 62]. Positive effects of IvIg may remain for up to a year [58]. One may speculate that there are different mechanisms behind the clinical effects of the treatment with IvIg and the effects of muscular resistance training. Thus, resistance training may enhance the positive effect of IvIg.

3.4 PHYSIOTHERAPY EVALUATION INSTRUMENTS

3.4.1 The Six-minute-walk test (6MWT) (I-IV)

The 6MWT is often used in physiotherapy for both clinical and scientific purposes to evaluate gait performance.

The 6MWT is a product of the 12-minute running test described by Cooper in 1968 [86]. Based on this, a 12-minute walking test proved to provide useful objective information about exercise tolerance in patients with chronic bronchitis [87]. That test provides a simple and practical guide to everyday disability. However, it was both time-consuming for the test leader and exhausting for the patient. For this reason Butland and colleagues [88] explored the possibility of using shorter walking tests to assess exercise tolerance. Three tests, of two-, six-, and twelve-minutes, correlated-highly, indicating that they were similar measures of exercise tolerance. Those authors also showed that the longer the patients walked, the greater was the spread of results. The differences were however not large. A learning effect of the 6MWT was later described and, thus, a prior familiarization of the test was recommended by Gibbons et al [89].

The 6MWT has been used in several evaluations of PPS patients [58-60, 63-66] and shows high reliability in this patient group [64-65]. In the study by Flansbjer and Lexell [64], the test was assessed twice, seven days apart. It was recommended for use in clinical practice as well as in research to evaluate gait performance and changes over time in patients with PPS. Another study [65], on PPS patients, found that 6MWT distance correlated with muscle strength and balance. In that study, the test was conducted three times separated by at least one day. Both studies showed small learning effects, i.e. the distance walked increased from test to test, however, without reaching significance [64-65]. The distance walked in six minutes also correlates with the physical dimension scores of the Sickness Impact Profile (SIP) and the Short-Form 36 (SF-36) in patients with PPS [63].

In Studies I and III, patients were told to perform the 6MWT at a speed they thought they could manage for six minutes, using their ordinary shoes and with their ordinary walking aid. The patient was informed that he or she was allowed to rest (the clock was not stopped) and would not receive any physical assistance. In Study I, evaluating the reliability of 6MWT, three tests with 30 minutes rest between each, were performed by the patients included.

In Study II and IV, when 6MWT were combined with 3D gait analysis, see below, patients were told to walk as far as possible during six minutes, at a self-selected speed. The patients were, also here, allowed to rest and were not given any physical assistance. They performed the test barefoot and without walking aids.

3.4.2 Gait analysis (II, IV)

Gait analysis can afford data invisible when gait only is inspected. Apart from spatio-temporal parameters such as cadence and step length, gait analysis also gives kinematic data such as joint angles during the gait cycle and also often kinetic data, electromyography (EMG) and digital video data. Joint kinematic and kinetic measures are reportedly more discriminative between groups with different walking capacity than gait speed alone, which has lower sensitivity [90]. This is considered in Studies II and IV, where the 6MWT was combined with 3D movement analysis. Earlier studies have used similar technologies in evaluation of knee-ankle-foot orthoses (KAFOs) during gait in patients with PPS [67-69]. However, no earlier comparison between patients with PPS and healthy controls regarding 3D movement analysis has been found in the literature.

Gait was analysed at the Human Physiological Laboratory Karolinska Institutet at Danderyd University Hospital. For 3D movement analysis an eight-camera Vicon MX System (Oxford, UK) was used. The present gait analysis session consisted of three parts: patient preparation, data recording and data analysis. The patients were prepared by attaching, 35 reflective markers to the skin, with double-sided tape, at anatomical positions, according to the Plug-In Gait Full Body model. With the markers attached, the subject performed the test. The cameras emit strobe light, which reflects back from the markers. The coordinate location of each marker is then calculated within the camera. The computer receives coordinates from all the cameras and tracks the markers to establish a 3D image. Spatio-temporal gait parameter data, here including walking speed, step length and cadence, were processed using the Plug-In Gait Full Body model (figure 3) and the Polygon 3.5.1 software. ASCII files of the kinematic data, here including ankle-, knee- and hip angles, in the sagittal plane, during parts of the gait cycle (see below), were analysed in AxoGraph 4.9 (Axon Instruments, Inc., Foster City, CA, USA) or in Microsoft Excel.

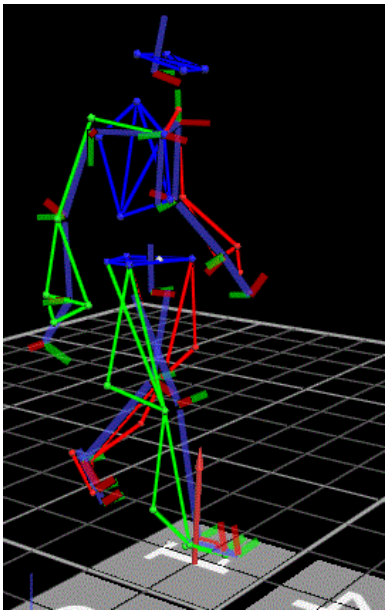

Figure 3. Registration of 3D movements.

Figure 4. The Human Physiological Laboratory Karolinska Institutet at Danderyd University Hospital.

The gait cycle starts with initial contact (IC), when one foot contacts the ground, or with heel strike. We chose the former since the heel is not always the first to touch the ground. The cycle ends when the same foot contacts the ground again [20]. In the stance phase, the foot is on the ground for 60% of the cycle, while in the swing phase, 40%, the foot is moving forward through the air. The stance phase ends, and the swing phase starts, when one foot leaves the ground, toe-off or foot-off (FO) [20]. In studies II and IV ankle-, knee- and hip angles, in the sagittal plane, during IC and FO of the same leg were analysed. Walking speed, step length and cadence were also analysed. Data were recorded for 7 s during the first and last 30 s periods of the 6MWT, respectively. A heart rate monitor (Polar), was used to evaluate heart rate before, during and after the test and the total distance walked was recorded.

In Study II, the PPS patient's most affected leg was compared to the mean value of the right and left legs of the healthy controls. In Study IV, the patient's most affected leg, based on isometric knee extension strength measured with Kin-Com, was used. If the most affected leg was too weak to perform the test, the other leg was used after neurophysiologic verification that it was affected by polio.

3.4.3 Dynamometer (III, IV)

Isokinetic, dynamometers are frequently used to assess muscle strength in both healthy populations and in difference diseases. With an electric or hydraulic servo-controlled mechanism, they provide constant velocity with accommodating resistance throughout the range of motion of a joint. The Kinetic Communicator (KinCom) (Kin-Com 125 E Plus, Chattecx Chattanooga, USA) and the Biodex dynamometer (Biodex Medical Systems, NY, USA) are common isokinetic dynamometers.

Several studies have used isokinetic dynamometers to evaluate muscle strength in patients with PPS [24, 66, 71-72, 74-76] and the test-retest reliability of isokinetic dynamometers in this patient group has been evaluated [70, 73]. In a study by Flansbjer et al [70], the reliability of knee-extensor and flexor-muscle strength measurements was assessed in 30 patients with PPS, using a Biodex dynamometer. The authors concluded that knee muscle strength can be measured reliably and can also be used to detect real changes after an intervention in a group of patients with PPS. In a study by Kilfoil et al [73], the reliability of isokinetic strength measurement was assessed in eight patients with PPS, using a Cybex dynamometer. The study showed that muscular performance of subjects with PPS, measured isokinetically, is reliable.

A KinCom dynamometer was used for measuring knee muscle strength in Studies III-IV. The patient sat (hip angle 90º) with their back against a backrest with a seatbelt strapped around the chest and the tested leg, and the ankle fastened to the dynamometer arm. The anatomical axis of the knee was aligned with the axis of the dynamometer, and the distal aspect of the dynamometer arm was placed 2 cm proximal to the medial malleolus. Dynamic knee muscle strength was measured at a velocity of 60º/sec with start force set to 15 N. Range of motion was 90–30º (Study III) (0º straight leg) and 90–10º (Study IV). Gravity was corrected for at 45º. A warm-up session immediately preceded the test (in Study III, a learning session within a week before the test was added).

In Study III, three maximal knee extensions, with one minute of rest between each, were performed to evaluate maximal peak torque. Muscle endurance was measured by recording total work (J), during 50 repeated maximal knee extensions at a velocity of 120º/sec and with a passive return at a velocity of 60º/sec.

In Study IV, three consecutive maximal knee extensions and flexions were performed and total work (J) of the repetitions was evaluated. Maximal isometric strength was measured at 60° knee flexion. Three consecutive extensions and flexions respectively were performed. Each trial lasted five seconds, with a rest of one minute between the trials.

3.4.4 The Five-times-sit-stand-sit test (FTSST) (III)

The FTSST (in Study III referred to as the Sit-stand-sit test (SSS)) was used according to Whitney et al [91]. The patient is observed and timed while rising from a chair and sitting down again five times with arms crossed over the chest [91]. In patients with balance disorders, the FTSST has been described as a discriminative and valid test, useful in clinical decision-making [91]. Whitney et al [91] have shown that the FTSST is capable of identifying people with balance disorders. The test (Sit-to-stand test/Timed-stands test where the test was performed during ten seconds and ten times respectively) can be used to assess lower-extremity strength in elderly patients and in patients with rheumatoid arthritis and other chronic diseases [92-93].

3.4.5 The Timed-up-and-go test (TUG) (III, IV)

The TUG test is a reliable and valid test for quantifying functional mobility [94]. The test was performed according to Podsiadlo and Richardson [94]. The patient is observed and timed while rising from a chair, walking three metres, turning around, walking back and sitting down on the chair again [94]. The TUG has been used for evaluating PPS patients in several studies [10, 59, 64, 66, 77] and has shown high reliability in this patient group [64].

3.5 RATING SCALES

3.5.1 Borg evaluation scales (I-IV)

The Borg CR-10 (Category Ratio) scale and the RPE (Ratio of Perceived Exertion) scale [95] are often used in connection with physical activity, exercise and before and after the 6MWT for evaluating different symptoms and sensations in patients with PPS [34, 37, 42], in subjects with other diagnoses and in healthy subjects.

The Borg CR-10 scale is suitable for determining subjective symptoms such as breathing difficulties, aches and pain. The scale ranges from 0 to10, where 0 represents “very, very weak” and 10 as “very, very strong”. The Borg RPE scale is used for evaluating perceived exertion and increases linearly with exercise intensity during work on a cycle ergometer [80]. The values range from 6 to 20.

The Borg CR-10 scale was used in Studies I-IV for evaluating dyspnoea and leg tiredness and the Borg RPE scale for evaluating exertion. Both scales were used immediately before and after each performed 6MWT.

3.5.2 The Swedish Short Form-36 (SF-36) (III, IV)

SF-36 is a commonly used health-related quality of life measurement [96] and is translated into Swedish [97-98]. The questionnaire groups 35 items into eight dimensions: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). The sum score of each dimension is calculated and transformed so that the lowest and highest possible values are 0 and 100. A higher score indicates better health status. The SF-36 has been used in several studies for evaluating quality of life in PPS patients [46, 59-61, 63, 77-78].

3.5.3 The Physical Activity Scale for the Elderly (PASE) (IV)

The PASE is a reliable and valid instrument to assess physical activity in epidemiological studies of elderly persons [99-100]. Its ten questions measure physical activity over a one week period. Scores range from 0 to 400, where a higher score indicates more physical activity [101]. The PASE has been used in earlier studies of PPS patients [19, 59, 61].

3.5.4 The Multidimensional Fatigue Inventory (MFI) (IV)

MFI is a 20-item self-report instrument [102]. It is designed to measure fatigue and covers General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Minimum and maximum scores for each item are 4 and 20, respectively. A higher score indicates greater fatigue. The instrument evaluates self-report fatigue during the previous days. The MFI has been translated into Swedish and is reported as a valid and reliable instrument for measuring fatigue in different patient populations and in healthy individuals [103]. The questionnaire has been used in earlier studies of PPS patients both in evaluation of interventions [46, 59] and in studies examining characteristics of fatigue [15, 17].

3.5.5 The EQ5D (IV)

The EQ5D measures health outcome and is intended to supplement other quality of life measures [104]. It consists of three question each on mobility, hygiene, main activities, pain and anxiety/depression and a visual analogue scale (VAS) for self-reported current health status. The EQ5D has been used for describing and following up health-related quality of life in the general population in Stockholm [105-106] and is today commonly used by the Stockholm County Council.

3.5.6 Visual Analogue Scale (VAS) (IV)

The VAS is described by Huskisson [107] as the most sensitive method for measuring pain. Zero on a 100mm scale represents no pain and 100 represents the worst imaginable pain [108]. The VAS has been used, for measuring pain intensity in PPS patients [18-19, 79] in studies evaluating IVIG treatment [57, 59, 62] and identifying responders to IVIG treatment [61].

3.6 ETHICS AND STATISTICS

All four studies included in this thesis were approved by the Regional Ethical Review Board in Stockholm, Sweden (table 5).

Table 5. Registration number for each study included.

Study	Ethical approval, Registration number
I	2011/1270-31/1
II	2010/1883-32
III	2005/1517-31/2
IV	2010/97-31/3

An overview of the statistical methods used appears in table 6. The IBM SPSS Statistics program (version 14 or 20) was used for calculation of data. $P < 0.05$ was considered as statistically significant. Descriptive statistics were used to present patient characteristics and results i.e. mean and standard deviation (SD), median and quartiles (25% and 75%) and minimum and maximum values, 95 % confidence interval (CI), frequency and percentage. Bland Altman plots [109], where the difference of two measurements for an individual subject is plotted against their mean, were used in Study I for visualising systematic bias and outliers in the 6MWT results.

Table 6. Overview of statistical methods used.

	Study I	Study II	Study III	Study IV
$ICC_{2.1}$	X			
Repeated Measures, ANOVA	X			X
Independent samples *t*-test		X		
Paired samples *t*-test		X		
Wilcoxon Signed Ranks test		X	X	X
Mann-Whitney test		X	X	X

4. RESULTS, DISCUSSION AND CONCLUSIONS

4.1 STUDY I

In this intra-rater test-retest reliability study 23 PPS patients completed three 6MWT. Nine patients walked unaided. The group with walking aids included nine using a stick or a crutch when walking, three walking with two sticks or two crutches and two using a walker.

In earlier evaluations of the reliability of the 6MWT in PPS patients [64-65], the tests were assessed with at least one-to-seven days between each. The present study evaluated the possibility for patients with PPS to perform three 6MWT the same day, which, in the outpatient clinic, is more practical for both patients and staff.

Individual distances walked varied from 140 m to 395 m, and the mean ± SD was, for test 1: 266 ± 72 m, test 2: 268 ± 79 m and test 3: 270 ± 80 m. The distance increased from test 1 to test 3 also for the sub-groups walking with or without walking aids. Patients who walked without walking aids walked further than those with.

The reliability of the three 6MWT appears in table 7. The intra-class correlation coefficient ($ICC_{2.1}$) describes how strongly units in the same group resemble each other. Our $ICC_{2.1}$ values were here high, indicating high reliability [110] . Based on these data, one 6MWT would be enough, for evaluation of gait performance, at least for a clinical purpose. The standard error of measurement (SEM) represents the smallest change that indicates a real change for a group of individuals, and the smallest real difference (SRD) represents the smallest change that indicates a real change for a single individual. Both SEMs and SRDs were reasonably small, implying that the 6MWT has acceptable sensitivity and can be used to detect real clinical changes in a group as well as in an individual. However, a small learning effect was seen, since only eight of 23 patients had their first test as the best. Thus, for more precise evaluation of gait performance, for example in research, two tests would be preferable.

Table 7. Reliability of two occasion measures in the Six-minute-walk test (6MWT) for the whole group of patients (n=23), without walking aids (n=9) and with walking aids (n=14).

6MWT	$ICC_{2.1}$	95% CI	SEM (m)	SEM (%)	SRD (m)	SRD (%)
Whole group n=23						
T1-T2	0.98	0.95 - 0.99	12	4.4	33	12.2
T2-T3	0.99	0.97 - 0.99	9	3.4	26	9.5
Without walking aids n=9						
T1-T2	0.97	0.89 – 0.99	14	4.6	39	12.7
T2-T3	0.99	0.99 – 0.99	5	1.5	13	4.2
With walking aids n=14						
T1-T2	0.97	0.91 – 0.99	9.9	4.1	27	11.3
T2-T3	0.96	0.89 – 0.99	11.6	4.6	31	12.8

$ICC_{2.1}$ = intra-class correlation coefficient; CI = confidence interval;
SEM = standard error of measurement; SRD = smallest real difference.

The differences in evaluation of exertion, dyspnoea and leg tiredness (Borg RPE and CR-10 scales respectively) between the tests were small, both for all participants and for the sub-groups. The $ICC_{2.1,}$ values increased while the SEM and the SRD values decreased from T1-T2 to T2-T3 for the whole group and for the group without walking aids. However, the opposite was seen for the group with walking aids (see table 7). This indicates an increase in fatigue in the later tests for the group using walking aids. Based on this, thirty minutes is regarded as a minimal time for recovery for this patient group. As the present patients had fairly maintained walking ability, the present results, should be generalized only to this patient category. One way to further explore fatigability in this patient category would be a longer walking period e.g. using the 12-minute walk test (12MWT).

According to the American Thoracic Society (ATS) guidelines [111] for the 6MWT patients are instructed to walk as far as possible for six minutes and regularly encouragement are included during the test. However, instructions for the 6MWT differ between different studies [59, 64, 111-113]. The present subjects were told to walk at a speed they thought they could maintain for six minutes and were not given any encouragement from the test leader during the test, taking into account the risk of overstrain and overuse, as described in polio patients due to clinical weakness and asymmetric paresis [40-41]. However, to evaluate endurance adequately, subjects should be instructed to cover as much ground as possible during the six minutes i.e. reach the maximum walking speed. One may anticipate longer walking distance and a higher exertion rate with the latter instructions.

In conclusion, our data indicated that the 6MWT is considered reliable for subjects with PPS, as in previous studies. The present results also indicated that the patients with walking aids became fatigued during the later tests. Given the high reliability it may be enough to perform one test. As mentioned above, however, the study showed a small learning effect and therefore the best results of the two tests can be used for research purposes.

4.2 STUDY II

In Study II gait analysis based on registration of 3D movement during the 6MWT, was performed for 18 PPS patients and 11 healthy controls. The two groups were equal regarding gender and age. Differences in the spatio-temporal and kinematic gait variables were evaluated. Data were collected at the beginning and end of the 6MWT to detect influence of fatigue.

The mean ± SD distance walked during the 6MWT was for the controls 441 ± 51 m and for the patients 229 ± 88 m. This difference reached statistical significance ($p<0.001$).

The PPS patients experienced more leg tiredness and dyspnoea, but equivalent exertion, after the test, compared with the healthy controls. However, the PPS patients estimated their exertion much higher than did the healthy controls before the test started. There were no statistically significant differences between the groups regarding heart rate at rest or during the test.

All the spatio-temporal gait parameters differed significantly ($p<0.001$) between the groups both at the beginning and the end of the 6MWT, with lower values in the patient group. This was anticipated as the PPS patients had lower muscle strength. Both PPS patients and controls was slowing down during the 6MWT with a considerably more pronounced decrease in walking speed, cadence and step length in the PPS group. This indicated greater fatigability in the PPS group than in the healthy controls. In the PPS group, fatigability was also seen in the kinematic data. This was because only in the PPS patients, both hip and knee flexion at FO significantly correlated fairly well with perceived exertion, at the end of the test ($r=0.47$, $p<0.05$, in both cases). In addition the PPS patients' walking speed correlated moderately strongly inversely with both perceived exertion and leg tiredness following the 6MWT ($r=-0.65$ and $r=-0.62$, $p<0.01$), while for the controls, walking speed only correlated with perceived exertion following the 6MWT ($r=0.62$, $p<0.05$).

Ankle angle at IC and hip- and knee angles at FO differed statistically significantly between the groups both at the beginning and at the end of the 6MWT. At IC the ankle was plantar-flexed in the majority of the PPS patients but dorsal-flexed in the majority of the controls ($p<0.001$). Further, three PPS patients had an ankle angle less than -10 degrees at the start and end. This was anticipated, as drop-foot is often seen in this patient group.

Perry et al [114] have shown that ankle plantar flexion strength has an important role in gait, affecting cadence and velocity. Ankle plantar flexion strength provides the "push off" in the FO part of the gait cycle, moving the leg into the swing phase. As plantar flexion torque was not measured, plantar flexor function cannot be excluded as a limiting factor for walking speed in PPS patients. However, no correlations between the increases in ankle plantar flexion angle at FO and impaired walking cadence or walking speed were detected in the patients.

Instead, the most striking finding of the study was related to the hip joint, as the hip, at FO, was flexed in the patients while extended in the controls (p<0.001). Also only in the PPS patients, walking speed and cadence was fairly well to moderately strongly correlated inversely with hip flexion at FO both at the beginning (r=-0.60, p<0.01; r=-0.54, p<0.05) and at the end (r=-0.74, p<0.001; r=-0.52, p<0.05) of the test. Why the relationship between hip extension during gait and walking speed was so robust in the PPS patients cannot be answered on the basis of the present data. It is mechanically feasible that hip extensors would be important to maintain gait speed, e.g. by assisting the advance of the contralateral leg [115]. Accordingly, reduced hip extension has been suggested as a functionally significant gait impairment in the elderly, exaggerated in weak elderly people [116]. In PPS patients, it is conceivable that due to distal muscle weakness, the range of neuromuscular adaptations available to counteract the reduced hip extension, is more limited than shown in weak elderly individuals in general. As dorsal flexion strength was not measured, it cannot be excluded that the flexed hip compensated for weakness in dorsal-flexion and drop-foot moving the leg forward in swing phase without dragging the foot along the floor.

Thus it cannot be stated from the present results whether rehabilitation focused on the hip will be important in PPS. One may, however, hypothesize that the deficient hip extension noted in our PPS patients is of clinical significance, and that physiotherapy programmes focusing on strengthening hip muscles might increase gait function, e.g. increased step length and walking speed of PPS patients.

In conclusion, the 6MWT is a fatiguing test for PPS patients. A distinct plantar-flexed ankle at IC was seen in the PPS patients together with significantly more flexed hip and knee at FO compared with the controls. The 3D results underscore the importance of hip function in this patient group.

4.3 STUDY III

In this randomized placebo-controlled study 14 PPS patients were included. They were selected for either resistance training combined with oral supplementation with Q10 (200 mg/day) or resistance training combined with placebo treatment.

After training, for all the patients, muscle strength (measured with SSS and an isokinetic dynamometer) had increased statistically significantly (p=0.010 and p<0.05 respectively) as had muscle endurance (measured with 6MWT) (p<0.05) and mental health (measured with SF-36) (p=0.05). There were, however, no statistically significant differences between the Q10 and the placebo group for any of the evaluations.

As in several previous studies [8, 23-24, 32-38], our results show that PPS patients have positive effects of resistance training. The improved 6MWT result in the Q10 group might suggest increased muscle endurance. However, the results of the other tests including total work during muscle endurance (measured with an isokinetic dynamometer) did not support this assumption. One reason for the positive results on mental health might be the positive effects of training in a group several times per week, meeting others in the same situation and the positive atmosphere in the group.

Given the recommendations to PPS patients to avoid overexertion, the subjective feeling of pain and fatigue was taken into careful consideration and individual changes from the exercise programme were made. For the same reason, it was in some cases hard to test 1RM and the workload was then based on the patient's muscle strength, earlier workload and subjective feeling.

There are uncertainties in this kind of study where the patients themselves take supplementation with drugs/placebo. The small number of subjects makes it hard to draw any absolute conclusions about the effect of Q10, as the effect may differ from one person to another. The groups were not matched for gender or age. Further, the study spans a relatively short time, so we cannot draw any conclusions regarding long-term effects of supplementation with Q10.

In conclusion, no beneficial effect of Q10 supplementation on muscle function or quality of life in patients with PPS was seen. The result confirmed that muscle training leads to increased muscle strength, muscle endurance i.e. walking distance and mental health.

4.4 STUDY IV

Study IV was a clinical, open prospective study. Seventeen PPS patients received treatment with IvIg (90 g) (15 included in gait analysis). A sub-group performed a 12-week muscular resistance training programme.

After the 12 weeks for all the participants, walking distance during 6MWT increased statistically significantly (p= 0.041), while walking speed and cadence tended to increase (p=0.077 and p=0.067, respectively). Isometric knee flexion strength had increased (p=0.044) after the 12 weeks. This corroborates earlier findings i.e. increase of muscle strength and physical activity as a result of IvIg treatment in PPS patients as reported by Gonzalez et al [59].

Decreased hip- (p=0.006) and knee- (p=0.001) flexion at FO were seen after the 12 weeks compared with pre-treatment. Only the hip angle at FO correlated moderately strongly with walking distance (r=-0.761, p<0.001) and walking speed (r=-0.696, p<0.004) including cadence (r=-0.671, p<0.006) and fairly well with step length (r=0.579, p<0.024), at the beginning of the pre treatment test. The correlation between decreased hip flexion at FO and increased walking speed corroborates findings seen in study II. These correlations disappeared after 12 weeks. However, in accordance with study II, one may speculate that interventions should focus on increasing hip muscle strength in PPS patients, as increased strength here may lead to a decrease in hip flexion angle and an amelioration of gait function.

During the 6MWT, fatigability was seen i.e. decreased walking speed both pre-treatment and after 12 weeks. A tendency (p=0.065) towards decreased leg tiredness, at the end of the test was seen after the 12 weeks compared with pre treatment. Despite increased walking distance, no differences were seen regarding fatigue i.e. heart rate, exertion or dyspnoea, indicating that IvIg does not decrease fatigability in the short perspective of 12 weeks.

In earlier studies, treatment with IvIg has shown positive effects regarding quality of life [59-60] and pain [57, 62] in PPS patients. This was not found in the present study, except for increased general health in the training group. One explanation may be the low number of participants with pain included in the study (ten patients reported pain with intensity 20 mm or more on VAS pre-treatment). This pain sub-group showed, however, a tendency (p=0.057) to a decrease in pain intensity after IvIg treatment compared to pre-treatment. The present results do not support earlier speculations by Gonzalez et al [59] that a decrease in pain could be the primary effect of IvIg treatment, leading to increased muscle function. In addition, we saw no correlation between pain intensity and walking distance.

One hypothesis in the study was that effects of training and IvIg treatment have different backgrounds and a combination of these would lead to improving the individual results. Whether muscle training enhances the effect of IvIg cannot be fully answered on the basis on the present data, since the gender distribution was skewed, the number of patients training was low and the training group proved, even before treatment, to have statistically significantly greater isometric knee strength than the

group on IvIg treatment alone. However, in the training sub-group, a further increase in walking distance was seen after 12 weeks compared to pre treatment (p=0.030). When comparing the groups, improved general health (SF-36) (p=0.020) and less general fatigue (MFI-20) (p=0.036) were also seen in the training group after the 12 weeks. In addition they showed a tendency towards increased muscle strength i.e. total work during isokinetic knee extension and flexion strength, regarding the difference between baseline and after the 12 weeks (p=0.096 and p=0.083 respectively). The results of training resembled earlier reported effects, although a more pronounced effect was anticipated. The results may be explained by the skewed distribution of the patient material or to a possible common background for the effects of IvIg and training.

Studies of IvIg treatment in PPS patients include both responders and non-responders to IvIg treatment. This leads to difficulties in interpretation of results. Main indicators for identification of responders of IvIg treatment have recently been reported [61] as age below 65 years, paresis in the lower extremities and absence of concomitant disorders. In future studies including only responders to IvIg treatment, one would have a more accurate conclusion as to whether IvIg alone, or in combination with training, has a clinical effect.

Individual changes from the exercise programme were also made in this study, as in Study III, following the recommendations given to PPS patients to avoid overexertion.

In conclusion IvIg treatment in PPS patients leads to an increased walking distance and hip flexion angle most probably due to increased muscle strength. The additional training had some further positive effects, which may be due to the skewed distribution of the patient material or may be due to a common background of IvIg and training. Based on the present results it is obvious that one should only include PPS patients who are responders to IvIg in order to obtain adequate data on the clinical effect of IvIg. The physical training should be focused, as discussed in Study II, on increasing muscle strength and stabilization in the hip.

5. GENERAL DISCUSSION AND CONCLUSION

5.1 POLIO AND POST-POLIO

In my experience, there is a general belief that polio no longer exists, especially in Sweden and in the younger population. However, according to the Post-polio Health International, there are 12-20 million people with sequelae of poliomyelitis in the wold today and in the Swedish population the estimated number of polio patients is 15 000-20 000 (according to RTP [4]). This makes it one of the most common disorders with neurological deficits, and it is still endemic in a few countries. In Sweden, as in many other countries, increasing numbers of patients with sequelae of poliomyelitis are immigrants and young people. The high number of patients with sequelae of polio, in some cases with severe affection of function, certainly warrants further scientific studies. Due to individual differences in the effects of acute poliomyelitis the need for rehabilitation interventions differs. Further, a sub-group of patients will develop PPS with increasing neurological deficits and increased need for medical and rehabilitation interventions. However, it is as important to recognize interventions in patients with sequelae of polio as in PPS patients.

Further, PPS patients may serve as a model for other disorders with lower motor neuron lesions, such as neuropathies and muscle diseases. Thus it is of great importance to study PPS patients to increase our knowledge of adaptive and compensatory phenomena. This knowledge may serve as a background for tailoring physical interventions in both PPS patients and other patients with sequelae of polio, as well as in those with other lower-motor-neuron disorders.

5.2 GAIT ABILITY

PPS patients have a subjective feeling of reduced balance and fear of falling [13, 117]. This might be due to weakness in lower-limb muscles [5, 9] and compensatory changed motor unit characteristics [21-24, 26-27, 29, 118], which may also decrease their ability to rapidly avoid obstacles when walking. The 6MWT has shown high reliability in PPS patients and is often used for evaluating gait performance and physiotherapy interventions. As shown in Study I it is sufficient to perform the 6MWT once. It may, as shown in Study II, be used in combination with 3D gait analysis, to enable detection of data invisible when only gait is inspected.

Except from the plantar-flexed ankle at IC, seen in the majority of the PPS patients, the most striking finding from the present gait analysis was the generally larger hip flexion in PPS patients than in healthy controls, most evident at FO, where the hip was flexed in the patients while extended in the controls. In the PPS patients only, hip extension at FO correlated with walking speed. Muscle weakness in lower leg muscles and drop-foot are often seen in this patient group and the gait analysis was here performed without orthosis, i.e. ankle dorsal-extension orthosis. As dorsal flexion strength was not measured, it cannot be excluded that the generally large hip flexion compensated for weakness in dorsal-flexion and drop-foot moving the leg forward in swing face without dragging the foot along the floor. Peak hip extension is, however, shorter in elderly

fallers compared to non-fallers and is the only kinematic finding in elderly people, exaggerated in fallers [116]. The alterations in gait pattern i.e. reduced hip extension seen in PPS patients, may, as in the elderly, impair balance and thereby cause fear of falling. Few regular activities in daily life extend the hip to its maximum, thereby stretching the hip flexors. Thus, based on this, physiotherapy interventions aiming at a general increase in muscle power in the lower extremity, and with focus on hip muscle stability and muscle strength, may have clinical value in walking distance, speed and balance. The physiotherapy interventions may thus reduce falls and the fear of falling. They should therefore be recommended in PPS patients.

5.3 EXERCISE AND MUSCLE WEAKNESS

Physically active patients with PPS have shown significantly lower odds of experiencing polio-related late muscle pain and fatigue than those not often physically active [39]. Physiotherapeutic interventions, such as physical activity and muscle training, are the basis for rehabilitation of PPS patients [5]. The present training results add evidence that exercise has several positive effects on muscle strength, quality of life (here regarding mental health and general health), and fatigue, in PPS patients. Based on this, an active lifestyle should be recommended for patients with polio sequelae. However, this is not without problems since PPS patients have asymmetric paresis which may lead to both over- and low use of muscles in the same patient, and low muscle strength in an overexerted muscle is not suitable for physical exercise. Individually-planned training programmes are therefore of great importance. The patient's subjective feeling of pain and fatigue should be taken into careful consideration, following the recommendations given to PPS patients to avoid muscle overuse (exertion to the point of muscle pain and fatigue) both in daily living and in exercise. There are, however, no prospective studies proving that increased muscle activity or training in polio patients leads to loss of muscular strength compared with the absence of training or less muscular activity.

New symptoms may force patients to physical inactivity, leading to a vicious circle. Why physically active patients have lower odds for late polio-related symptoms is not clear. One explanation may be the beneficial changes both physiologically and psychologically of physical activity in general.

5.4 MEDICAL INTERVENTIONS

The earlier positive effects of Q10 in PPS patients were not reproduced in Study III, there being no beneficial effect of Q10 supplementation on muscle function or quality of life. However, long-term effects of supplementation with Q10 have not been evaluated.

The results of the IvIg treatment in Study IV were in line with results from earlier studies [59]. IvIg had a positive effect including increased walking distance, increased isometric knee flexion strength and decreased hip- and knee flexion angle at FO. A characterization of responders is ongoing and preliminary characteristics have been reported [61]. In future studies, which should only include responders to IvIg, more

precise data are anticipated concerning the outcome of the treatment in PPS, since only about one-third of PPS patients are responders to IvIg, i.e. have positive effects of the treatment.

IvIg treatment in combination with training resulted in a further increase in walking distance as well as improved general health (SF-36) and less general fatigue (MFI-20), compared with the group only receiving IvIg treatment. More similar groups including only responders to IvIg and a larger number of participants would be required to give a more accurate conclusion as to whether IvIg in combination with training, has a clinical effect.

5.5 CONCLUSION

- 6MWT is a reliable test for evaluating gait ability in PPS patients. One test may be enough for clinical purposes, but the best results of two tests can be used in research.
- Compared to healthy controls, PPS patients walk with plantar-flexed ankle at IC and an increased hip flexion at FO. The latter negatively correlated with walking speed.
- Muscle training has positive effects in PPS patients regarding walking ability i.e. walking distance as well as muscle strength and mental health.
- Q10 supplementation showed no beneficial effect on muscle function or quality of life in patients with PPS.
- After IvIg treatment, increased walking distances, isometric knee-flexion strength, and decreased hip- and knee flexion at FO were found.
- IvIg, in combination with training, gave a further increase in walking distance as well as improved general health and less general fatigue.

5.6 CLINICAL IMPLICATIONS

The 6MWT, which is a reliable test for evaluating gait ability in PPS patients, may be performed once for clinical purposes.

It is suggested that physiotherapy interventions focused on the function of the hip may improve gait ability, such as increased step length and walking speed, in patients with PPS. Physiotherapeutic interventions aimed at increasing muscle strength in the lower extremity, focusing on hip function i.e. strength- and stabilizing exercise may also prevent falls.

Supplementation with Q10 cannot be recommended in PPS patients, according to study III.

As in previous studies IvIg showed positive effects in patients with PPS. IvIg in combination with muscle training showed further positive effects. Further studies are, however, needed to fully answer whether muscle training enhances the effect of IvIg.

5.7 FUTURE RESEARCH

Based on the results of Studies II and IV, a future project should include PPS patients in three groups, one performing resistance training, one receiving treatment with IvIg and one receiving treatment with IvIg in combination with resistance training. Only responders of IvIg are planned to be included.

A training programme, focused on range of motion (ROM), strength- and stabilizing exercise for muscles around the hip, is to be developed and evaluated.

An ongoing research project aims to evaluate the frequency of falls, and to collect clinical data so as to increase the knowledge of fear of falling and consequences of falling in patients with PPS.

Gait analyses are often performed barefoot, without walking aids, as also done in the present work. Different kinds of orthosis and walking aid are, however, often used by PPS patients. Using gait analysis for evaluation of PPS patients' gait, with their usual walking aids and orthoses and/or in validation of new walking aids and orthoses would, therefore, be of great interest and give knowledge about their ordinary gait performance.

A research project already started aims to evaluate the 2-, 6- and 12-MWT in PPS patients. Twenty PPS patients are planned to participate in the study, performing 2-, 6- and 12-MWT, with one week between each. It is hypothesized that patients with PPS with different levels of paresis may show muscle fatigability when performing the different tests. Thus, 2-, 6- and 12-MWT should probably be applied in different patient groups.

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