From the Division of Rehabilitation Medicine, Department of Clinical Sciences, Danderyd University Hospital Karolinska Institutet, Stockholm, Sweden

ASPECTS OF FATIGUE IN POST-POLIO

Gunilla Östlund

Stockholm 2010
To my late parents

Rolf and Eila
Fatigue is a subjectively experienced and complex phenomenon and one of the most common symptoms of post-polio syndrome (PPS) occurring in up to 90% of patients. Experiencing fatigue negatively affects work performance, family life, social relationships, and quality of life (QOL). Fatigue can originate in the central or peripheral nervous system and can be experienced in various ways, for example as general, physical, mental, or muscle fatigue.

The overall aim of the thesis was to evaluate and analyse fatigue in PPS patients. The specific aims were as follows: to determine whether generally fatigued PPS patients display cognitive deficits compared with non-fatigued subjects; to evaluate vitality and fatigue and the relative effects of physiological and psychological parameters on the vitality level; to characterize fatigued and non-fatigued PPS patients, and to define subgroups across the fatigue continuum; and finally, to describe QOL characteristics as measured using the SF-36 instrument in responders and non-responders after intravenous immunoglobulin treatment (IVIG).

The research examines three samples of PPS patients. Study I includes twenty PPS patients, with and without general fatigue recruited from the post-polio out-patient clinic at Huddinge University Hospital, Stockholm. Studies II and III analyse baseline data for 143 PPS patients from a Swedish multicenter study, and Study IV is based on follow-up data for 112 patients from the post-polio out-patient clinic at Danderyd University Hospital, Stockholm, before and after IVIG treatment.

No cognitive performance differences could be detected between the fatigued and non-fatigued PPS patients, and systematically varying the test order did not cause significant mental fatigue. Vitality in PPS patients was mostly dependent on physiological rather than psychological parameters, and mental fatigue was not a prominent predictor. Contrary to expectations, vitality increased while fatigue and pain decreased with increasing age. Fatigued PPS patients were characterized by significantly lower age, more physical problems and lower QOL than were non-fatigued PPS patients. Furthermore, in the fatigued group, mental fatigue was relatively more important than was physical fatigue. In the total sample of PPS patients, the scores for the SF-36 subdomains Vitality, Bodily pain, Social function, Role-emotional and Mental compound score (MCS) significantly improved after IVIG treatment at the six-month follow-up. Vitality and Bodily pain were identified as possible outcome variables for IVIG treatment and positive-, non-, and negative responders were identified. Positive responders for treatment were characterized by a low vitality i.e., high fatigue, before treatment.

It is concluded that, in PPS, fatigue is mostly physical in nature – mental fatigue not being a prominent phenomenon – and that general fatigue does not affect cognition. PPS patients, of whom fatigued PPS patients can be considered a subgroup, may respond positively or negatively to IVIG treatment. PPS patients with high levels of fatigue and pain before treatment are the ones who may benefit from the IVIG treatment.

Keywords: post-polio syndrome, general fatigue, physical fatigue, mental fatigue, vitality, cognition, subgroups, quality of life, IVIG, response group.
Fatigue är ett subjektivt fenomen, komplext till sin karaktär och ett av de vanligaste symptomen vid post-polio syndromet (PPS). Upp till 90% av PPS patienter kan uppleva fatigue. Fatigue har en negativ påverkan på livskvalitet i allmänhet, familjeliv, sociala relationer och även på arbetsförmåga. Fatigue kan emanera både från det perifera och det centrala nervsystemet och kan upplevas på olika sätt av individen, t ex som en generell, fysisk mental eller muskel relaterad fatigue.

Det övergripande syftet med denna avhandling har varit att utvärdera och analysera fatigue hos PPS patienter. Mer specifika syften har varit: att undersöka om PPS patienter med generell fatigue skiljer sig åt från dem utan generell fatigue när det gäller kognitivt fungerande; att undersöka om kognitiv belastning, definierat som en variation i testordning påverkade den kognitiva prestationen: att utvärdera vitalitet och fatigue och det relativa bidrag som fysiologiska och psykologiska parameterar har på nivån av vitalitet; att karaktärisera PPS patienter med och utan fatigue samt att beskriva livskvalitet, men framförallt vitalitet, utvärderat med SF-36, hos PPS patienter som svarar respektive inte svarar på intravenös immunoglobulin behandling (IVIG).

Tre olika grupperingar av PPS patienter utgjorde grunden för detta arbete. I studie I ingick 20 PPS patienter med och utan generell fatigue från post-polio mottagningsanläggning på Huddinge Universitets sjukhus. I studie II och III analyserades grunddata från 143 PPS patienters som ingick i en Svensk multicenter studie. Studie IV slutligen, baserades på uppföljningsdata från 112 PPS patienter från post-polio mottagningsanläggningen på Danderyds Universitets Sjukhus före och efter behandling med IVIG.

Inga skillnader i kognitiv prestation kunde ses mellan PPS patienter med och utan fatigue och ett systematiskt varierande av testordningen kunde inte signifikant provocera fram mental fatigue (studie I). Vitalitet hos PPS patienter var till större delen beroende av fysiologiska snarare än psykologiska faktorer och mental fatigue verkade inte vara av betydelse för variationen i vitalitet (studie II). Tvärtom mot vad som kan förväntas så ökade vitaliteten med ökande ålder och upplevelsen av smärta minskade med ökande ålder hos PPS patienter som deltog i studien (studie II).


Slutsatserna är att fatigue i PPS till största delen kan definieras som fysisk fatigue. Generell fatigue påverkar inte det kognitiva fungerandet hos PPS patienter och mental fatigue verkar inte heller vara ett framträdande problem. PPS patienter med en hög nivå av fatigue skulle kunna utgörä en undergrupp. Bland de PPS patienter som fått IVIG behandling finns både positivt och negativt utfall vad beträffar vitalitet och det verkar främst vara de PPS patienter med hög fatigue och smärtnivå som är lämpligast att behandla med IVIG.

**Keywords:** post-polio syndromet, generell fatigue, fysisk fatigue, mental fatigue, vitalitet, kognition, livskvalitet, IVIG.
LIST OF PUBLICATIONS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals.


CONTENTS

1 INTRODUCTION ........................................................................................ 1
  1.1 Poliomyelitis ....................................................................................... 1
    1.1.1 A viral disease ........................................................................1
    1.1.2 Polio-survivors - in the world, Europe and Sweden.............. 1
  1.2 Post-polio syndrome (PPS) ................................................................. 2
    1.2.1 Polio survivors with PPS ........................................................2
    1.2.2 The most common symptoms of PPS ....................................2
    1.2.3 Less frequent symptoms ......................................................... 3
  1.3 Fatigue ................................................................................................. 3
    1.3.1 Fatigue in healthy individuals ................................................3
    1.3.2 Fatigue types ...........................................................................3
    1.3.3 Fatigue related to disease .......................................................3
    1.3.4 Fatigue and age.......................................................................4
    1.3.5 Fatigue measurements ............................................................4
  1.4 Fatigue in PPS ..................................................................................... 5
    1.4.1 Prevalence of fatigue in PPS ..................................................5
    1.4.2 Fatigue in PPS ........................................................................5
    1.4.3 Mental/brain fatigue in PPS ...................................................5
    1.4.4 Physical fatigue in PPS ..........................................................6
    1.4.5 An inflammatory process in PPS ...........................................6
  1.5 Other causes of fatigue in PPS ........................................................... 6
    1.5.1 Mental health ..........................................................................6
    1.5.2 Fatigue and pain - muscle and joint pain in PPS ....................7
    1.5.3 Sleep problems and sleep disordered breathing and fatigue . 7
    1.5.4 Working and fatigue and PPS ................................................8
    1.5.5 PPS related, non-PPS related and normal fatigue .................8
  1.6 Consequences of fatigue ..................................................................... 9
    1.6.1 Neuropsychology ..................................................................9
    1.6.2 Cognitive domains ..................................................................9
  1.7 Treatment of fatigue in PPS .............................................................10
    1.7.1 Coping ...................................................................................10
  2 AIM OF THE THESIS ...............................................................................11
  3 SUBJECTS AND METHOD .....................................................................12
    3.1 Study population ...............................................................................12
    3.2 Inventories and tests .........................................................................14
      3.2.1 Inventories ............................................................................14
      3.2.2 Neuropsychological assessments .........................................15
    3.3 Procedures .........................................................................................17
      3.3.1 Study I ...................................................................................17
      3.3.2 Study II ..................................................................................17
      3.3.3 Study III ...............................................................................18
      3.3.4 Study IV ...............................................................................18
    3.4 Statistics ............................................................................................19
      3.4.1 Statistical methods used in studies I – IV ............................19
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck’s Depression Inventory</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>FIS</td>
<td>Fatigue Impact Scale</td>
</tr>
<tr>
<td>FSS</td>
<td>Fatigue Severity Scale</td>
</tr>
<tr>
<td>FQ</td>
<td>Fatigue questionnaire</td>
</tr>
<tr>
<td>IVIG</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental compound score</td>
</tr>
<tr>
<td>MFI-20</td>
<td>Multidimensional Fatigue Inventory 20, questions</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>PASE</td>
<td>Physical Activity Scale for the Elderly</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical Compound Score</td>
</tr>
<tr>
<td>PPS</td>
<td>Post-polio syndrome</td>
</tr>
<tr>
<td>RAS</td>
<td>Reticular activation system</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>SDB</td>
<td>Sleep-disordered breathing</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form-36</td>
</tr>
<tr>
<td>SQS</td>
<td>Sleep Quality Scale</td>
</tr>
<tr>
<td>TMT</td>
<td>Trail-making test</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WAIS-R</td>
<td>Wechsler Adult Scale of Intelligence, revised</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 POLIOMYELITIS

1.1.1 A viral disease

Poliomyelitis is a contagious viral infection. In most cases, it produces no symptoms and immunization occurs in the infected person. In 4–8% of cases, polio produces mild, flue–like symptoms, such as fever, sore throat, nausea, or diarrhoea, from which patients may recover fully. However, in approximately 5% of infected individuals, the central nervous system (CNS) is involved, leading to deterioration of anterior horn cells and paralysis or weakness in one or more muscle groups. If respiratory muscles are affected the patient experiences acute hypoventilation and needs assisted ventilation (WHO poliomyelitis key facts, Bach 2004). The death rate in the group with the most severe cases is 4–10% (Melnick 1996).

After an acute phase, characterized by muscle weakness, there is a recovery phase during which motor units are reinnervated by means of collateral sprouting; this results in increased muscle power, which in some cases may lead to a full recovery of function (Halstead & Rossi 1987). In many cases, the recovery is incomplete, leaving patients with residual weaknesses (Dalakas 1995). The recovery phase lasts from several weeks to several years (Melnick 1996) and is followed by a stable phase during which ongoing deinnervation is compensated for by reinnervation and other compensatory mechanisms such as muscle fibre transformation and muscle fibre hypertrophy (Gonzalez et al. 2010). After the stable period new or increased muscle weaknesses or other symptoms may occur due to uncompensated deinnervation (Grimby et al. 1998), a condition called the post-polio syndrome (PPS).

1.1.2 Polio-survivors - in the world, Europe and Sweden

There are approximately 12–20 million polio survivors in the world today (Post-polio Health International) an estimated one million of whom are in Europe (European Polio Union). The last epidemic in Sweden was in 1953 with approximately 5000 cases: survivors of this epidemic are now in their fifties and sixties and many are still working. However, with increasing immigration, Sweden is today home to younger polio survivors as well.
1.2 POST-POLIO SYNDROME (PPS)

Various diagnostic criteria are used for post-polio syndrome (PPS): The ones most commonly used today are formulated by the March of Dimes (Table 1).

**Table 1.** Post-polio syndrome diagnostic criteria (March of Dimes 2001)

1. A confirmed history of polio and evidence of motor neuron loss.
2. After the acute period a period of complete or partial functional recovery and a period of 15 years or more of stable neurological function.
3. After the stable period, gradual or sudden onset of new muscle weakness or muscle fatigability. Generalized fatigue, muscle atrophy and muscle and joint pain may also be present. Less common are swallowing and breathing problems.
4. At least a year of persisting symptoms.
5. Other medical, neurological and orthopaedic problems are excluded.

1.2.1 Polio survivors with PPS

The proportion of polio survivors who will develop PPS is estimated to be from 20% to 68% in various studies (Dalakas, 1995, Grafman, 1995, Nollet et al. 2002, Codd et al. 1985). This considerable range may be due to the use of different diagnostic criteria or differences between study populations. The number of individuals with PPS in Sweden has been estimated to be 186/100 000, with the absolute number estimated to be between 7700 and 15700 (Ahlström et al. 1993).

1.2.2 The most common symptoms of PPS

The three most common PPS symptoms are muscle weakness, fatigue, and muscles and joint pain (Gawne & Halstead 1995, Jubelt 2004, Trojan et al. 2005). New muscle weakness occurring in both previously affected and unaffected muscles has been reported in up to 87% of the PPS patients (Lonnberg 1993, Agre et al. 1989, Halstead & Rossi 1985, Halstead & Rossi 1987, Halstead 2004) while fatigue occurs in up to 89% of PPS patients (Codd et al. 1985, Halstead & Rossi 1987, Schanke & Stanghelle 2001). Up to 86% of PPS patients suffer from muscle pain (Gawne & Halstead 1995) and up to 80% report joint pain (Vasiliadis et al. 2002).
1.2.3 Less frequent symptoms

Other less common symptoms associated with PPS are muscle atrophy, cold intolerance, respiratory insufficiency and dysphagia (Jubelt 2004, Gonzalez et al. 2010).

1.3 FATIGUE

1.3.1 Fatigue in healthy individuals

Fatigue is defined in several ways. Fatigue can be described as a negative feeling regarding one’s capacity to perform physical or mental activities (O’Connor & Puetz 2004) or a state of tiredness, strain and weakness associated with feelings of exhaustion (Tralongo 2003). An epidemiological study (Lewis 1992) of one million individuals found that one fourth of the population experienced feelings of fatigue that interfered with their lives (Lewis & Wessely 1992). According to Åhsberg et al. (2000) healthy individuals perceive fatigue after mental work as a lack of energy, lack of motivation, and increased sleepiness. Physical activity can improve or worsen feelings of fatigue, depending for example on the amount and intensity of the activity (O’Connor 2004).

1.3.2 Fatigue types

General fatigue is an umbrella term for all sorts of fatigue of various origins and natures. Fatigue can be divided into central fatigue, including mental fatigue, and peripheral fatigue, including physical fatigue. Central fatigue involves the central nervous system (Borg 2004, Davies & Walsh 2010) and can be caused by primary affection of the CNS, such as head injury, stroke or multiple sclerosis, or be secondary to mental effort, stress, or depression. Individuals experiencing mental fatigue often have difficulties in areas involving information processing speed and planning (Johansson et al. 2009). One powerful perceptual stimulus that can lead to mental fatigue is pain, which demands attention and competes with other stimuli (Grigsby et al. 1995).

Peripheral fatigue involves the peripheral nervous system and the muscles (Kirkendall 1990) and may be experienced as physical fatigue (Cantor 2010). However, a muscle that does not receive an optimal signal from the CNS does not develop maximal force and may suffer from CNS-related fatigue (Zwarts 2007), so some peripheral fatigue may involve both central and peripheral mechanisms (Davis & Walsh 2010).

1.3.3 Fatigue related to disease

Fatigue is common in various psychological and physical conditions and illnesses, such as depression and anxiety (Henningsen 2003, De Battista 2003), and in concomitant
disorders, such as cardiovascular disease (Tang 2010), sleep-disordered breathing (Hong 2003), stroke (de Groot 2003), cancer (Dimeo 1999), multiple sclerosis (Bakshi 2003), rheumatoid arthritis (Belza 1993), chronic fatigue syndrome (van Geelen 2010), anaemia (Agnihotri 2007), obesity (Vgontzas 1998) and chronic obstructive pulmonary disease (Theander 2004).

1.3.4 Fatigue and age

Increasing age is related to increased fatigue levels, individuals over 65 years old reporting significantly more fatigue than do younger individuals (Tralongo et al. 2003). A study by Schwarz et al. (2003) of a representative sample of the German population found that fatigue increased almost linearly with increasing age. In contrast, no direct relationship between increasing age and increasing fatigue was observed by Young et al. (2008) in a similar study; instead, individuals with co-morbidities reported increased levels of fatigue independently of age.

Physical fatigue may also increase with age. Healthy individuals lose functional motor units and motor neurons with increasing age, especially after the age of 60 (Galea 1996).

1.3.5 Fatigue measurements

Fatigue is a subjective experience and may therefore be difficult to measure. The simplest way to measure fatigue is to use a visual analogue scale (VAS) (Mollaoglu et al. 2010, Gencay-Can & Can 2010). Self-report instruments can evaluate and assess fatigue, and several fatigue inventories and scales, both single and multidimensional (Dittner 2004), are used to measure various aspects of fatigue. Some of these have been used to measure fatigue in PPS (Table 2). One such instrument is the Multidimensional Fatigue Inventory (MFI-20; Smets & Garssen 1994), which is constructed around five scales measuring various aspects of fatigue. The Fatigue Severity Scale (FSS) comprises nine statements about fatigue using seven-point Likert scales (Krupp et al. 1989). The Fatigue questionnaire (FQ) is an 11-item questionnaire measuring both physical and mental fatigue and was developed for epidemiological studies (Chalder et al. 1993). The Fatigue Impact Scale (FIS) consists of 40 statements covering cognitive, physical and psychosocial functioning over the previous four weeks (Fisk et al. 1994). Finally, the health-related quality-of-life (QOL) Short-Form 36 (SF-36) inventory includes a Vitality sub-domain, which covers aspects of fatigue (Ware et al. 1993). Research for the present thesis uses the Swedish version of the SF-36 (Sullivan 1995, 1998).
Table 2. Fatigue inventories and scales used in PPS populations.

<table>
<thead>
<tr>
<th>Fatigue inventories</th>
<th>Example of studies</th>
<th>This thesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidimensional fatigue inventory 20 questions (MFI-20)</td>
<td>Trojan et al. (2009), Gonzalez et al. (2006)</td>
<td>X</td>
</tr>
<tr>
<td>Fatigue Questionnaire (FQ)</td>
<td>Schanke et al. (2001, 2002)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue Impact Scale (FIS)</td>
<td>On et al. (2006)</td>
<td>-</td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
<td>Schanke et al. (20029)</td>
<td>X</td>
</tr>
<tr>
<td>Short Form-36 (SF-36)</td>
<td>Schanke et al. (2001), Gonzalez et al. (2006)</td>
<td>X</td>
</tr>
</tbody>
</table>

1.4 FATIGUE IN PPS

1.4.1 Prevalence of fatigue in PPS

Fatigue was reported by 59–89% of studied PPS patients (Codd et al. 1985, Halstead & Rossi 1987, Schanke & Stanghelle 2001) and was multidimensional in character. The general fatigue perceived by the PPS patients may be divided into mental fatigue and physical fatigue (Trojan et al. 2009). There are two causes of fatigue in PPS, a central and a peripheral cause, in which central fatigue is traceable to the CNS and peripheral fatigue to the peripheral nervous system, i.e., the motor units (Borg 2004).

1.4.2 Fatigue in PPS

General fatigue in PPS is often described as a flue-like exhaustion, worsened by physical activity that does not resemble the fatigue experienced by individuals without PPS. The level of PPS-related fatigue is low in the morning but increases over the course of the day; it is often related to a decreased ability to concentrate and an increased need for naps (Trojan & Cashman 2005).

1.4.3 Mental/brain fatigue in PPS

Polio survivors reportedly suffer from brain or mental fatigue with symptoms such as deficient attention, concentration, information processing, lexical search, and non-verbal retrieval (Bruno et al, 1993, 2000). However, polio survivors with and without PPS performed equally well at attention, concentration, and memory tests compared to
matched controls in a study by Hazendonk et al. (2000). Bruno et al. (1994) found lesions in the reticular activation system (RAS) on MRIs of 55% of PPS patients with fatigue. However, Schanke et al. (2001) observed no differences in the experienced mental fatigue between male polio survivors and the normative male population.

1.4.4 Physical fatigue in PPS

Schanke et al. (2001, 2002) found physical fatigue to be the major problem experienced by PPS patients and suggested that it was of several origins; this was corroborated by the findings of Trojan (2009). PPS patients experience a cycle of deinnervation and compensatory reinnervation (see above) (Borg 1996). The loss of motor neurons probably starts directly after the acute polio infection and when uncompensated for, may be responsible for the increasing muscle weakness and fatigue in PPS patients (Gordon et al. 2004). In addition, the normal motor neuron loss found in healthy individuals over the age of 60 is also ongoing in PPS patients (Grimby et al. 1998, Borg 1996). Vasconcelos et al. (2007) and Chan et al. (2006) found Modafinil to be ineffective in PPS related fatigue, suggesting that it is physical in nature.

1.4.5 An inflammatory process in PPS

An inflammatory process may also play a role in the fatigue experienced by PPS patients. Increased cytokines in the cerebrospinal fluid of PPS patients, indicating an inflammatory process, has been reported by Gonzales et al. (2002, 2004), and other studies have reported inflammatory changes in peripheral blood (Fardyce 2008, Farbu 2007). The inflammatory process in the CNS of PPS patients was down-modulated by treatment with intravenous immunoglobulin (IVIG) (Gonzalez et al. 2004), which had a clinical effect on QOL, especially on the SF-36 sub domains of Vitality and General health, and also on muscle power (Gonzalez et al. 2006). Preliminary results of an Italian randomized, double-blinded, placebo controlled study of IVIG in 50 PPS patients was recently presented. A statistically significant improvement in fatigue was found (Borg K personal communication 2010). The inflammatory process might be a factor influencing both mental and physical fatigue in PPS patients.

1.5 OTHER CAUSES OF FATIGUE IN PPS

1.5.1 Mental health

Psychological conditions, in particular depression, which is also associated with fatigue (Leone 2010), can be more or less severe and may present problems with concentration, memory, and increased fatigability. Other depression symptoms include sleeping difficulties and feelings of worthlessness (Socialstyrelsen), and the more severe the
depression, the more common these symptoms. Risk factors for developing depression are a family history of depression and stressful life events; such life events include divorce, bereavement, life-threatening illness, trauma, or job loss (Chen et al. 2000).

The prevalence of depression was found to be 9% in a population-based study (Kroenke et al. 2009), while Kemp et al. (1999) found no significant differences in depression incidence between PPS patients and age-matched controls. However, Tate et al. (1993) found indications of depression in 15.8% of polio survivors, while Kemp and Krause (1999) found that 20% of PPS patients had elevated depression scores. In a study by Berly et al. (1991), BDI depression scores indicated mild to moderate depression symptoms in 23% of PPS patients. Fatigued polio survivors reported more mental health problems than did either polio survivors without fatigue or healthy controls (Schanke et al. 2002). Furthermore, polio survivors with depression had poorer health, more pain, lower QOL, and poorer coping strategies than did polio survivors who did not suffer from depression (Tate et al. 1993, 1994). Clark et al. (1994) found that PPS patients had normal psychological profiles, while Kemp et al. (1997, 1999) found that higher depression scores among PPS patients were more closely related to family support (defined as interaction, communication, adaptability and mutual support) and attitudes towards disability than to the PPS itself. This is in line with the results of a study by Thorén-Jönsson et al. (2001) in which PPS patients with a problematic family life reported an increased level of distress.

1.5.2 Fatigue and pain - muscle and joint pain in PPS

Willén and Grimby (1998) found that half of the PPS patients reported pain every day, mostly during physical activity. Women more often reported muscle and joint pain than did men in the study by Vasiliadis et al. (2002). Experience of fatigue and pain often co-occur. Nijrolder et al. (2010) examined changes in fatigue and pain over 12 months in a primary-care population with different diagnoses and problems, and found that pain improvement was associated with fatigue improvement. PPS patients with muscle pain reportedly had longer-lasting general fatigue, higher fatigue severity, and lower vitality than did PPS patients who did not report muscle pain (Vasiliadis et al. 2002). Pain is a common complaint in PPS patients (see above), and since it may have various origins, thorough pain analysis must be performed (Werhagen & Borg 2010).

1.5.3 Sleep problems and sleep disordered breathing and fatigue

Van Kralingen et al. (1996) found that nearly half of PPS patients reported disordered sleep, though sleep-disordered breathing (SDB), such as apnoeas and snoring, was no
more common than in the control group. However, Dahan et al. (2006) found sleep-disordered breathing in 65% of PPS patients with general fatigue problems, even among those who did not have bulbar or respiratory involvement during acute polio. According to Lichstein et al. (1997), sleepiness and perceived fatigue are independent phenomena. Furthermore, daytime sleepiness may not predict fatigue and, according to Pigeon et al. (2003), daytime sleepiness and fatigue are supposed to be different phenomena. Thus, the background and treatment of PPS associated sleep problems and fatigue may differ from each other.

1.5.4 Working and fatigue and PPS

According to Dalakas (1995), it is uncommon for PPS-related fatigue to hinder work. Farbu and Gilhus (1997) found that the employment rate among polio patients did not differ from the national rate in Norway, 63% of the polio patients being employed versus a national average of 65% (age-span 16–74 years of age). They were employed at the same rate as were their siblings up to the age of 40 years, after which fewer polio survivors were employed full-time (polio survivors 55% versus sibling group 69%) (Farbu & Gilhus 2002). However, Lønnberg (1993) found fewer PPS patients working full-time compared with the general adult population. Katen et al. (2010) identified three barriers to full work participation on the part of PPS patients: low social support, high physical work demands, and pain and fatigue. Fatigue may thus be an important factor affecting PPS patients’ ability to continue working.

1.5.5 PPS related, non-PPS related and normal fatigue

As pointed out above, many factors can affect the subjective experience of fatigue in PPS patients. First, there are problems and symptoms related to PPS itself, such as muscle weaknesses, accelerated loss of motor neurons, lack of reinnervation, sleep disturbance due to increased breathing problems, or an ongoing inflammatory process in the Cerebrospinal fluid (CFS). Second, there are concomitant disorders (see above) or fatigue related to various types of pain or depression with or without cognitive symptoms, such as impaired concentration, attention, and memory. Third, there is the normal fatigue found in healthy individuals perceived after mental work or physical activity, depending on the volume and intensity of activity. All these causes of fatigue could partly explain the presence of fatigue in PPS patients.
1.6 CONSEQUENCES OF FATIGUE
As pointed out above, experienced fatigue negatively affects work performance, it also affects family life and social relationships (Rosenthal et al. 2008), and reduced QOL in PPS patients (On et al. 2006).

1.6.1 Neuropsychology
Fatigue may negatively affect cognition and increase the perseveration level and planning time; however, fatigue does not affect the performance on simple memory tasks (van der Linden et al. 2002). Pain may negatively affect cognitive functioning, and individuals with increased pain levels often have reduced psychomotor speed, processing speed and attention capacity (Grigsby et al. 1995).

1.6.2 Cognitive domains
1.6.2.1 Mental speed
Mental speed (or cognitive speed / perceptual speed or mental process speed) can be defined as the amount of novel information that can be processed during a certain time period.

1.6.2.2 Verbal fluency
Verbal fluency is a sub-function of the semantic memory system (Lezak 1995). Both cognitive speed and memory are important factors affecting fluency (Kertesz 1990).

1.6.2.3 Episodic memory
Episodic memory is the memory system that is related to specific autobiographical events and episodes in time and space. To store such memories they must be encoded, a process that can be intentional or incidental. To access these memories, a person must be able to retrieve them; retrieving memories without using cues is more demanding than doing so using cues. Episodic memory is sensitive to both disease and injury; there is a strong link to level of education and a weaker link to age (Almkvist 2000).

1.6.2.4 Visuospatial ability
Visual ability is related to the identification of forms and contours in our environment and cannot be separated from spatial ability, which is the ability to put these forms in a spatial context. An important aspect of visuospatial ability is abstract visuospatial thinking (Bartfai 2000).

1.6.2.5 Semantic memory
The semantic memory is the memory system that stores knowledge and facts. A subcategory of this memory is the flow of words tested in verbal fluency tests, for
example naming cities or the ability to recite a poem. Semantic memory is generally insensitive to health problems whereas mental speed, verbal fluency, episodic memory, and visuospatial ability are (Almkvist 2000).

1.7 TREATMENT OF FATIGUE IN PPS
There are several treatment alternatives for fatigue in PPS. Lifestyle change has been recommended, including energy conservation techniques such as pacing, prioritizing, planning, and posture (Cole 2004). Daytime napping has also been recommended (Trojan et al. 2004). When sleep-disordered breathing is present, it can be treated using various kinds of assisted ventilation (Olofsson et al. 2009). Pain reduction by means of medication, physiotherapy, bracing, and weight reduction can be used to reduce the level of fatigue in the PPS patients (Gonzalez et al. 2010). One pharmacological treatment for PPS-related symptoms is treatment with IVIG, which has been demonstrated to improve the vitality level of PPS patients and to ameliorate their fatigue (Gonzalez et al. 2004, 2006, Kaponides et al. 2006).

1.7.1 Coping
Coping styles may be problem-focused or emotionally focused. When using a problem-focused strategy, the aim is to change the situation outside the individual. Such strategies include identifying the problems, generating alternative solutions and choosing and implementing the best alternative. Emotionally focused strategies aim to change the individual perceptions of the situation in order to reduce the emotional stress experienced; this can be done by avoidance, denial, and distancing from the situation, and may work early in a situation but not in the long run. Positively interpreting a negative situation may be a more efficient way to cope with emotional distress (Kalpakjian 2004). Response shift is a change in the self-evaluated meaning of a situation and may play a part in the coping with fatigue in PPS (Barclay-Goddard et al. 2009). Response shift involves three processes according to Sprangers and Schwartz (1999): first, there is a change in internal standard, second, a change in values, and third, a re-conceptualization of life in the new situation.
2 AIM OF THE THESIS

The overall aim of the thesis was to evaluate and analyze fatigue in PPS patients. The specific aims were:

I. To examine the extent to which general fatigue is associated with cognitive deficits among PPS patients, to determine whether these deficits are general or selective, and to determine whether cognitive performance among those suffering from PPS also varies as a function of increasing load, and if so, whether such effects are pronounced among patients with PPS and general fatigue.

II. To evaluate quality of life and the influence of various physiological and psychological parameters relevant to patients with PPS, and to examine potential determinants of physical fatigue, physical activity and pain.

III. To analyse the characteristics of fatigued and non-fatigued PPS patients and to evaluate the central and peripheral backgrounds of fatigue, defined as mental and physical fatigue.

IV. To identify responders and non-responders on the basis of perceived quality of life in a group of PPS patients who have received intravenous immunoglobulin (IVIG) treatment.
3 SUBJECTS AND METHOD

3.1 STUDY POPULATION

Background data on the study populations appear in table 3. The population in Study I was selected from the post-polio outpatient clinic at Huddinge University Hospital Stockholm, Sweden. The inclusion criteria were a PPS diagnosis according to the Halstead criteria (Halstead et al, 1987, 1995). Before the first appointment, potential subjects completed a questionnaire including a question about general fatigue. Twenty subjects were recruited, and using the fatigue question, the participants were divided into a “fatigue” and a “non-fatigue” group. There were 10 participants in each group, five men and five women in each group and both groups were matched according to age, sex and education level.

The study populations in Study II and Study III were identical. 143 patients participating in a multicenter study, taking place between 13 August 2002 and 24 June 2003 were selected (Gonzalez et al. 2006). The four inclusion criteria were: (a) 18–75 old and a prior polio infection, (b) appearance of new symptoms, such as increasing muscle weakness/difficulties/pain after a stable period of at least 15 years, (c) a variation in weight over the past five years of not more than ± 7 kilos: and (d) the ability to stand and walk several meters with or without walking aids. The study population in Study IV consisted of 112 patients diagnosed with PPS according to the March of Dimes (2001) criteria, at the post-polio outpatient clinic at Danderyd University Hospital, Stockholm, who had received one IVIG treatment between November 2005 and October 2009 and who were covered by both background data and six-month follow-up data.
<table>
<thead>
<tr>
<th></th>
<th>Study I fatigue</th>
<th>Study I non-fatigue</th>
<th>Studies II and III total sample</th>
<th>Study IV total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>143</td>
<td>112</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>60.6(9.7)</td>
<td>59.4(8.9)</td>
<td>60.2(9.7)</td>
<td>65(60-73) median(Q1-Q3)</td>
</tr>
<tr>
<td>Females, %</td>
<td>50%</td>
<td>50%</td>
<td>64%</td>
<td>54%</td>
</tr>
<tr>
<td>Education (years), mean (SD)</td>
<td>11.3(2.1)</td>
<td>11.4(3.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other diagnoses (not acute),</td>
<td>0.7(0.8)</td>
<td>0.7(0.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polio duration, years, mean</td>
<td>55.9(8.3)</td>
<td>52.1(3.7)</td>
<td>54.0(8.2)</td>
<td>-</td>
</tr>
<tr>
<td>Age at incidence of polio,</td>
<td>4.6(2.9)</td>
<td>7.3(9.3)</td>
<td>-</td>
<td>5(2-14) median(Q1-Q3)</td>
</tr>
<tr>
<td>VAS-pain, mean(SD)</td>
<td>16.0(21.5)</td>
<td>29.1(25.2)</td>
<td>27.9(24.0)</td>
<td>26(12-46) median(Q1-Q3)</td>
</tr>
<tr>
<td>BDI total, mean (SD)</td>
<td>10.5(5.5)</td>
<td>4.8(5.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>-</td>
<td>-</td>
<td>25.2(2.6)</td>
<td>-</td>
</tr>
<tr>
<td>Occupation employment rate</td>
<td>-</td>
<td>-</td>
<td>36.4%</td>
<td>-</td>
</tr>
</tbody>
</table>

BDI= Beck’s depression inventory, BMI= Body mass index,
3.2 INVENTORIES AND TESTS

Inventories and neuropsychological tests used in this thesis are presented in table 4.

Table 4. Overview of Inventories and Neuropsychological tests

<table>
<thead>
<tr>
<th>Study</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inventories</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becks depression inventory (BDI)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidimensional Fatigue Inventory-20 (MFI-20)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Form-36 (SF-36)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sleep Quality Scale (SQS)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual analogue scale (VAS) pain</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visual analogue scale (VAS) fatigue</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Physical Activity Scale for the Elderly (PASE)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuropsychological tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental speed: TMT A &amp; B (short version)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit cancellation</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency: FAS</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Categories</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Episodic memory: Recall/Recognition</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Categories</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Visuospatial ability: WAIS-R Block Design test</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mental rotation test</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Semantic memory: SRB:1</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>WAIS-R Information</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

TMT=Trail Making Test, WAIS-R=Wechsler Adult Scale of Intelligence, revised,
SRB 1= Word synonym test

3.2.1 Inventories

**BDI** is a self-assessment scale gauging the level of depression (Beck & Steer 1996) that is used for screening but not for diagnosis. It consists of 21 groups of questions, each comprising four statements concerning how the individual felt over the last two weeks. The values for the statements responses range from 0 to 3; the total minimum value is 0 and the maximum value is 63. In a clinical setting, a score of 0–13 is categorized as minimal depression, 14–19 as mild, 20–28 as moderate and 29–63 as severe depression.

**MFI-20** is a 20-item inventory measuring five dimensions of fatigue (Smets 1995); each statement on the inventory refers to an aspect of fatigue during the day. The
dimensions are General fatigue, Physical fatigue, Mental fatigue, Reduced motivation and Reduced activity. A higher score on a seven-point Likert scale indicates a higher degree of fatigue. MFI-20 is considered a reliable instrument for measuring fatigue in both patient populations and in healthy individuals (Hagelin et al. 2007).

*SF-36*, the health-related QOL inventory Short-Form 36, comprises 36 questions assessing eight QOL dimensions. The physical health dimensions are Physical functioning, Role-physical and Bodily pain. The psychological health dimensions are Social functioning, Role-emotional and Mental health, while Vitality and General health include dimensions of both physical and psychological health. A score of 0-100 is calculated for each dimension, a higher score indicating a better QOL (Sullivan 1995, 1998, Ware et al. 1993).

*SQS* consists of three questions concerning difficulty to falling asleep, waking up at night and worried sleep (Pehrsson 1994). A higher score on a four-point Likert scale indicates more sleeping problems.

The *VAS* scales are constructed as 100-mm scales for assessing the current subjective experience of pain or fatigue, where 0 mm represents no pain or fatigue and 100 mm the worst imaginable pain or fatigue (Huskinson 1974, Joyce et al. 1975).

*PASE* measures physical activity over a one-week period and is considered a valid instrument (Washburn et al. 1999). It consists of 10 questions, six of which concern participation in leisure activities. The answer alternatives are recorded as never/seldom (1–2 days a week), sometimes (3–4 days a week) and often (5–7 days a week). Activity duration is categorized as less than 1 hour, 1–2 hours, 2–4 hours, and more than 4 hours. Paid or unpaid work is covered by four questions and is recorded in hours/week. Type of work alternatives are given and are recorded as yes/no. Scores range from 0 to 400 or more and are calculated from weight and frequency values. A higher total score indicates more physical activity.

### 3.2.2 Neuropsychological assessments

In study I, the following neuropsychological tests were used for assessing the following cognitive functions.

#### 3.2.2.1 Mental speed

A shortened version of Trail Making Test A and B (TMT) were used (Reitan 1974). In TMT A, a sheet of paper presented to the test subject has circles numbered 1–13 depicted on it. The test subject is supposed to draw a line between the numbers in order
as fast as possible. In TMT B, the circles are labelled with numbers 1–6 and letters A–F. The test subject is supposed to draw a line while shifting between numbers and letters in order. Both the number of seconds needed to finish the task and accuracy are registered. TMT A focuses on mental speed whereas TMT B focuses on divided attention. The Digit cancellation test constitutes a sheet of randomly arranged numbers from 1 to 9. The time limit is 60 seconds, in which time the test person must mark with a cross, using a pen, as many number fours as possible; Numbers of correctly marked fours are scored (Diller 1974).

3.2.2.2 Verbal fluency
In FAS, subjects are asked to generate as many words as possible beginning with the letters F, A and S. The time limit for each letter is 60 seconds. In Category fluency test (animals/professions/grocery store items) the test subject is asked to list as many animals/professions/grocery store items as possible. The time limit for each category is 60 seconds; scores start at 0 and up in both types of tests (Lezak 1995).

3.2.2.3 Episodic memory
The first episodic memory test comprises 12 randomly chosen words. Each word is shown to the test subject and read aloud by the test leader. Immediately after the presentation the test subject is asked to recall as many words as possible. After recall, the 12 words are again shown to the test subject; this time intermixed with 12 distracter words. By subtracting incorrect from correct “yes” responses the score range on this test is –12 to +12 (Wahlin 1995).

In the second episodic memory test, 12 words belonging to four categories (i.e., professions, furniture, instruments and clothes) are presented. These words are shown to the test subject, and also read aloud by the test leader, in random order. Immediately after the presentation, the test subject is asked to recall as many of the words as possible. After the free recall, the test subject is presented with the four semantic category names and is asked to recall as many words as possible from each category (cued recall). The score range on this test is 0–12 (Bäckman 1995).

3.2.2.4 Visuospatial ability
The WAIS-R Block Design Test is a series of construction tasks to be completed using nine red-and-white blocks. Each task has a time limit. The test subject is shown a card and is supposed to construct with the blocks what is depicted on the card. The test starts with simpler tasks and proceeds to more difficult ones. The solution must be correct,
but the score can be higher if the test subject completes the tasks faster. The minimum score is 0 and the maximum score is 51 (Wechsler 1981).

The Mental Rotation Test comprises 20 items, each consisting of one criterion figure, two correct alternatives, and two distracter figures (Vanderberg 1971). The correct answer is always identical to the criterion figure but rotated in space. Two marks are given for two correct answers, one for one correct answer, and no marks are given for a correct/false or a false/false combination. The minimum score is 0 and the maximum score is 40. The time limit for the test is 10 minutes.

3.2.2.5 Semantic memory

SRB:1 is a Swedish word synonym test, seven minutes in duration with a score range of 0–30 (Nilsson 1997). WAIS-R Information is a general knowledge test with a score range from 0–29. Test results are strongly related to education and socio-economic status (Wechsler 1981, Bartfai 2000).

3.3 PROCEDURES

3.3.1 Study I

The 20 subjects were asked in writing if they wanted to participate in the study; potential subjects not interested in participating were replaced by other subjects meeting the inclusion criteria for that specific group.

The subjects met a psychologist on one occasion during two hours. Before being neuropsychologically tested, subjects were asked to complete a background inventory, BDI, and two VAS scales (assessing pain and fatigue). The test battery comprised ten tests covering five cognitive domains. Cognitive load was operationalized as test order and each test was assigned a number between 1 and 10. A total of 10 test orders were created, which were randomly distributed in each group. The VAS scale measuring fatigue was administered again after five tests and after the subjects had finished the test battery. Feedback was given if requested by the subjects.

3.3.2 Study II

The subjects in Study II are the same as in the multicenter study by Gonzalez et al. (2006). Baseline data were collected within one to five weeks, in which time the medical staff met the 143 subjects on two occasions. Background data were collected at the first meeting. At the second meeting, the participants were administered SF-36, MFI-20, SQS and VAS-pain tests. Since they were highly correlated, SQS variables were collapsed into a single variable labelled Sleep Quality Scale-Total (SQST).
The variables were divided into (1) a physiological category comprising Physical function and General health variable from SF-36: General fatigue, Physical fatigue, and Reduced activity (from MFI-20); VAS-pain and BMI; and (2) a psychological category comprising SF-36 Mental health and MFI-20 Mental fatigue. The Vitality variable from SF-36 was the main outcome variable and SQST was a clinical indicator in the final analysis. Hierarchical regressions examining the predictors of Vitality were performed using five models. The purposes of the models were as follows: model 1 – to examine the amount of variance in Vitality accounted for by General fatigue: model 2 – to examine the extent to which the variance explained by General fatigue could be accounted for by differences in (a) physiological and (b) psychological indicators; models 3 and model 4 – to examine the relative importance of physiological and psychological indicators; and model 5 – to examine the extent to which the same variation in vitality was accounted for by age, BMI, Occupational/Employment Rate and polio duration.

3.3.3 Study III
The baseline data in study III are the same as in study II. On the basis of percentile distribution, the sample of 143 subjects was subdivided into three groups, i.e., fatigued (26.6%, n=38), intermediate (47.6% n=68), and non-fatigued (25.6%, n=37), using the MFI-20 General fatigue variable. Variables considered clinically relevant were selected. These were: Physical fatigue and Mental fatigue (from MFI-20); Physical functioning, Vitality, and Mental health (from SF-36); SQST, VAS-pain, Age, Gender, polio duration, and BMI. The number of participants who contracted polio after polio vaccine was introduced in Sweden in 1956 was calculated. Information about Occupational/Employment Rate was collected via medical records. Subjects over 65 years old were excluded from the statistical analysis, to enable calculation of the number of participants in the labour market.

3.3.4 Study IV
PPS patients at the post-polio outpatient clinic at Danderyd University Hospital were selected for IVIG treatment by a physician. Before treatment, they completed a standardized inventory comprising SF-36, VAS-pain, and PASE. The first follow-up was at six months ± three months and the second at 12 months ± three month. At each follow-up the patients again completed the standardized inventory, which was sent in. There were no overlaps in time between the follow-ups. Only patients with one IVIG
treatment covered by both background data before treatment and six-month follow-up data were included, for a total of 112 patients.

Because fatigue, pain, and muscle weakness are the most common symptoms of PPS, Vitality, Bodily pain and Physical functioning (from SF-36) were chosen as the outcome variables. To detect a difference of 10 points in these variables within one group, the recommended sample size is 28 subjects for Vitality, 36 for Bodily pain and 35 for Physical function (Sullivan 1995, 1998, Ware et al. 1993). Testing for significant differences in these variables between the time of treatment and the six-month follow-up indicated that both Vitality ($p = 0.006$) and Bodily pain ($p = 0.002$) were significantly different. The different outcome groups were all large enough to supply sufficient power. The study sample with Vitality as the outcome consisted of 110 subjects, with Bodily pain of 112 subjects, and with Physical functioning of 109 PPS subjects. The outcome variables were divided into three groups: positive responders (score increase of 11 or more points), non-responder (score increase or decrease of 10 or fewer points) and negative responders group (score decrease of 11 or more points).

3.4 STATISTICS

3.4.1 Statistical methods used in studies I – IV

- Descriptive statistics using mean and standard deviation or median and percentiles were used in all studies.

- Two tailed Pearson correlation (studies I and II) and Spearman non-parametric tests (Study III) were used.

- Analysis of variance (ANOVA) was used for comparison of the two groups in study I, and both ANOVA and Tukey tests were used for comparison of the three groups in study III.

- ANCOVA was used in study I for the main analyses, in which the effects of group and test order were examined after controlling for BDI scores.

- Hierarchical regression analysis using Vitality as the outcome variable was performed in study II.

- A significance test of the critical correlations between Mental fatigue and Physical fatigue (from MFI-20) and Vitality (SF-36) was performed across the three groups in study III.
• The chi² test was used to compare Occupational/Employment Rate between groups in study III and to compare of Gender between groups in study IV.

• Linear and non-linear regression were used to evaluate any differences in the strength of associations between Mental fatigue and Physical fatigue, on one hand, and Vitality on the other, in each of the three groups in study III.

• Kruskal-Wallis non-parametric tests were used for comparison between groups over time in study IV.

3.4.2 Treatment of scales in study I – IV

The tradition of using ordinal data (e.g. a Likert scale) as if they were interval data (Svensson 2001) was followed in studies I, II and III; however, in study IV, the data treatment was more in line with statistical recommendations (Svensson 2001).

3.5 ETHICS

3.5.1 Study I – IV

The studies included in this thesis and all procedures used were approved by the Ethics committee at Karolinska Institutet and by the Ethical Review Board in Stockholm, and were conducted in accordance with the Helsinki Declaration of 1975.
4 RESULTS AND DISCUSSION

4.1 STUDY I

ANOVA revealed no significant differences between the fatigued and the non-fatigued groups in terms of descriptive variables. However, BDI score were significantly higher in the fatigued group than in the non-fatigued group.

Subjective fatigue (measured using VAS) was analysed using a 2 (Group) by 3 (Time) repeated measurement ANCOVA. The Group (p < 0.05) and Time (p < 0.01) interactions, but not Group by Time interaction (p > 0.20) had significant effects.

The main effect of Group was because the fatigued group reported higher levels of subjective fatigue (mean, 59.9) than did the non-fatigued group (mean, 27.7), while the main effect of Time was because both groups reported increasing levels of subjective fatigue during the cognitive assessments (Figure 1).

![Subjective fatigue before, in the middle of and after the test situation in the fatigued and non-fatigued groups.](image)

There were no significant effects of BDI, Test order, Group, or Test order by Group, on cognitive performance measures (all p > 0.05). However, even though Time had no significant effects, β values indicated poorer performance late during a test. In some cognitive tests, the fatigued group performed better than the non-fatigued group (Table 5).
Table 5. Summary of cognitive performance statistics across groups.

<table>
<thead>
<tr>
<th>Cognitive variables</th>
<th>Fatigue mean(SD)</th>
<th>Non-fatigue mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter fluency FAS</td>
<td>42.2(12.6)</td>
<td>40.7(7.6)</td>
</tr>
<tr>
<td>Category fluency D/Y/M</td>
<td>61.8(22.1)</td>
<td>59.9(17.8)</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>14.9(5.2)</td>
<td>12.2(2.9)</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>29.9(24.8)</td>
<td>28.6(10.2)</td>
</tr>
<tr>
<td>Digit cancellations</td>
<td>18.8(4.3)</td>
<td>17.8(4.5)</td>
</tr>
<tr>
<td>Free recall, random words</td>
<td>7.3(1.2)</td>
<td>7.7(1.6)</td>
</tr>
<tr>
<td>Recognition, random words (hits-false alarms)</td>
<td>8.5(2.4)</td>
<td>9.7(1.4)</td>
</tr>
<tr>
<td>Free recall organisable words</td>
<td>7.8(1.9)</td>
<td>7.9(2.4)</td>
</tr>
<tr>
<td>Cued recall organisable words</td>
<td>8.5(1.7)</td>
<td>8.6(2.2)</td>
</tr>
<tr>
<td>WAIS-R Block design</td>
<td>28.0(9.5)</td>
<td>30.7(8.4)</td>
</tr>
<tr>
<td>Mental rotation</td>
<td>12.1 (8.0)</td>
<td>15.5(9.2)</td>
</tr>
<tr>
<td>SRB:1</td>
<td>24.2(3.2)</td>
<td>25.6(1.9)</td>
</tr>
<tr>
<td>WAIS-R Information</td>
<td>20.6(3.2)</td>
<td>21.9(2.5)</td>
</tr>
</tbody>
</table>

D/Y/M=animals/professions/grocery store, WAIS-R=Wechsler Adult Scale of Intelligence Revised, SRB 1=Word synonym test.

No significant differences were noted and the main finding was that mental or brain fatigue could not be triggered by altering the test order.

It is not clear why there was a lack of difference between the two groups. Possibly, this test battery was inappropriate for detecting mental/brain fatigue. Van der Linden et al. (2003) found that fatigue induced increased perseverance on the Wisconsin Card Sorting Test (WCST) and prolonged the planning time on the Tower of London test in healthy fatigued versus healthy non-fatigued subjects, though simpler memory tasks were unaffected. The inclusion of a healthy control group would have supplied valuable additional information, aiding the interpretation of the results. One cannot therefore conclude that PPS patients do not have cognitive impairment – a matter that has been considerably debated. Another limitation of the study is that the number of subjects in each group was low, which means that the statistical power is low: even though the groups were matched on the basis of age, gender and education, the mean differences had to be fairly large to be statistically significant.
4.2 STUDY II

In the total study sample, 36.4% of subjects worked at least 25% of full-time. Including only participants aged 24–65 years increased the employment rate to 65%, which is less than the 80.8% rate for the total Swedish population.

When all variables included in the study were correlated, increasing Vitality was found to be associated with better QOL and less pain but, surprisingly also with increasing age. Increasing age, on the other hand, was not only associated with increasing Vitality but also with decreasing General fatigue and Mental fatigue, decreasing pain and better General health and Mental health.

Five models were included in the first set of hierarchical regressions examining predictors of Vitality.

- In model 1, General fatigue accounted for 68.5% of the variance in Vitality.
- In model 2, 91% of the above variance explained by physiological and psychological variables together, of which Physical fatigue and Mental health had the largest explanatory power.
- In model 3, after controlling for age and when the physiological block of variables was entered before the psychological block, the physiological block accounted for 56.6% and the psychological block for 13.4% of the variation in Vitality.
- In model 4, after controlling for age and when the psychological blocks of variables were entered first, the physiological block accounted for 24.9% and the psychological block for 38.7% of the variation in Vitality.
- In model 5, Age, BMI, Occupation/employment rate and polio duration together accounted for 10.8% of the General fatigue-related variance in Vitality, of these factors, only Age and BMI contributed significantly.

The next set of hierarchical regressions performed examined predictors of Bodily pain, Reduced activity, and Physical fatigue.

With pain as the dependent variable Physical fatigue, Reduced activity, Age and Sleep Quality Scale – Total (SQST) together accounted for 90.2% of the variation in pain. Significant contributions were made by Physical fatigue (β 0.442), Age ((β –0.174) and SQST (β 0.268).
With Reduced activity as the dependent variable, Polio duration, BMI, Bodily pain, Age and SQST together accounted for 39.1% of the variation in Reduced activity and BMI ($\beta 0.177$), pain ($\beta 0.258$), and SQST ($\beta 0.220$) made a significant contributions.

With Physical fatigue as the dependent variable, Polio duration, BMI, Bodily pain, Age and SQST together accounted for 79% of the variation in Physical fatigue. BMI ($\beta 0.198$), Bodily pain ($\beta 0.409$) and SQST ($\beta 0.198$) made significant contributions.

The most important variable explaining variation in Vitality was General fatigue; however, 32% of the variation in Vitality was unaccounted for. The physiological block of variables explained more than did the psychological block, and mental fatigue was of minor importance to the experience of Vitality experienced by PPS patients. It may be that Vitality in PPS is more dependent more on physiological than psychological parameters. Not only Vitality but also Bodily pain may be dependent on physiological parameters. Physical fatigue, Age, and sleep quality together explained one third of the variation in pain in the PPS patients. Furthermore increasing age was associated with decreasing pain. In the correlations, age was also significantly associated with higher Vitality, better Mental health, and less General and Physical fatigue. The finding that fatigue is mainly physical in nature is in accordance with the results obtained by Trojan et al. (2004) but runs counter to the data presented of Bruno et al. (1994, 1995) who suggested that mental fatigue in PPS patients was secondary to CNS affection. Notably, the general assumption of decreasing vitality and increasing fatigue and pain with increasing age does not hold for PPS patients; on the contrary, vitality generally increases while pain and fatigue decreases, probably due to effective coping mechanisms such as response shift (see above chapter 1 7 1).

4.3 STUDY III

There were no significant differences between the three groups regarding gender distribution. However, members of the fatigued group were significantly younger, had shorter polio duration, lower Vitality, more Physical fatigue and Mental fatigue, more Bodily pain, and poorer Mental health than did the intermediate and non-fatigued groups. The fatigued group had a significantly higher BMI than the non-fatigued group. No significant differences in physical activity as measured by using PASE were seen between the three groups.

When all those over 65 years old were excluded, there were no significant differences between the three groups in terms of employment rate.
In the fatigued group, 18.4% had contracted polio after 1956 versus 2.9% in the intermediate group and no one in the non-fatigued group.

In the total sample \((n = 143)\) General fatigue was highly correlated with Vitality \((r_s = -0.837, p < 0.0001)\), increased General fatigue being associated with decreased Vitality. A significance test of the relationship of Mental fatigue and Physical fatigue (from MFI-20) with Vitality indicated that the correlation between Mental fatigue and Vitality differed significantly between the fatigued and non-fatigued groups \((p = 0.0257)\). Physical fatigue and Vitality did not differ significantly across groups, but there were tendencies towards significance between the fatigued and non-fatigued groups \((p = 0.0615)\) and the fatigued and intermediate groups \((0.0777)\).

Correlations between the clinically important variables Vitality, VAS pain, Physical fatigue and Mental fatigue were performed in the fatigued, intermediate and non-fatigued groups. The number of correlations between these variables and the others included in the study decreased with increasing fatigue.

Mental fatigue explained 9.8% and Physical fatigue 5.9% of the variation in Vitality in the fatigued group, 11.9% and 39.9% in the intermediate group, and 18.9% and 45.6% in the non-fatigued group, respectively. Mental fatigue had a relatively higher explanatory value than did Physical fatigue in the fatigued than in the intermediate and non-fatigue groups.

The fatigued group differed from both the intermediate and the non-fatigued groups, for example in being younger. Schwartz et al. (2003) found an almost linear increase in general fatigue with increasing age in a general German population. In addition, motor neurons are lost with increasing age, especially after the age of 60 so it was expected that the fatigued group in the presented study would be older. This was not confirmed; instead, the older patients were found in the non-fatigued group, possibly due to successful adaptation to and coping with the new situation.

The fatigued group had more Physical fatigue and Mental fatigue than did the other two groups. However, Mental fatigue was relatively more important than Physical fatigue for the variation in Vitality in the fatigue group. In the other two groups, the pattern was reversed. This is in accordance with the findings of study II, i.e., increased vitality with increasing age. Vitality correlated with the other QOL variables in an expected way in the intermediate and the non-fatigued groups. Such relationships are also evident in a study by Åkerstedt et al. (2010), who found disordered sleep to be an
important predictor of fatigue, and in a study by Nijrolder et al. (2010), where an increase or decrease of fatigue was directly related to an increase or decrease of pain.

The patients in the fatigued group, on the other hand, displayed no such correlations and may thus, on the basis of increased fatigue and the absence of expected correlations with demographic factors, constitute a subgroup of PPS patients. Further study is needed and may reveal whether this is due to biological factors or, for example, to contextual or concomitant factors.

### 4.4 STUDY IV

In the total sample, there were significantly increased scores at the six-month follow-up for the SF-36 sub-domains Vitality, Bodily pain, Social functioning, Role - emotional and MCS compared with before treatment. At the 12-month follow-up the score for Bodily pain was still improved.

There were no significant differences in terms of gender or age between the various response groups for any of the outcome variables. Kruskal-Wallis non-parametric tests for comparison between groups indicated that, with Vitality as the outcome variable, there were significant differences between positive, non- and negative responders before treatment in Vitality, Role - emotional, MCS (from the SF-36), and at the six-month follow-up in Role - physical, General health, Vitality, Social function, Mental health, physical compound score (PCS) and mental compound score (MCS) (from SF-36). With Bodily pain as the outcome, there were significant differences between the three responder groups before treatment only in Bodily pain and, at the six-month follow-up, in Bodily pain and PCS. Finally, with Physical functioning as the outcome variable, group differences were seen before treatment and at the six-month follow-up in Physical functioning and PCS.

A comparison of median scores between positive and negative responders for each outcome variable revealed opposite patterns. With Vitality as the outcome variable the positive responders had a median score of 33 before treatment, 65 at the six-month follow-up and 50 at the 12-month follow-up. This pattern was the opposite in the negative responder group. The median scores were 53 before treatment, 28 at six-month follow-up and 45 at the 12-month follow-up. This pattern was also seen when only complete data available for all three occasions were included (Figure 2).
Figure 2. Vitality as outcome, including only complete data for all three occasions. Median score across groups over time.

Figure 3. Bodily pain as outcome, only complete data at all three occasions included. Median score across groups over time.

With Bodily pain as the outcome variable positive responders had a median score of 41 before treatment, 62 at the six-month follow-up and 51 at the 12-month follow-up. The negative responders had a median score of 61 before treatment, 41 at six-month follow-up, and 51 at the 12-month follow-up. The pattern was confirmed when the sample was restricted to PPS patients with complete data available at all three occasions (Figure 3).
Figure 4. Physical function as outcome, only complete data at all three occasions included. Median score across groups over time.

With Physical functioning as the outcome variable, the Physical functioning scores were 30, 63, and 38 for the positive responders and 70, 35, and 40 for the negative responders at the time of treatment and at the six- and 12-month follow-ups, respectively, even here the pattern was confirmed by data when only complete data from all three occasions were included (Figure 4).

There were different response combinations for the three outcome variables. Some of the PPS patients responded positively in at least two outcome variables. Twenty PPS patients responded positively in both Vitality and Bodily pain, eight in Vitality and Physical functioning, and nine in Bodily pain and Physical functioning. However, some PPS patients responded negatively in at least two outcome variables: five PPS patients responded negatively in both Vitality and Bodily pain, two in Vitality and Physical functioning and two in Bodily pain and Physical functioning. The other responses included a positive or a negative response in combination with a non-response.

The present results are in accordance with those of Kaponides et al. (2006) and Gonzalez et al. (2004, 2006), i.e., IVIG has a positive effect at the group level when PPS patients are treated. However, the present study found the effect to be more obvious in the mental than the physical sub domains, possibly due to the use of different inclusion criteria in the different studies. In the present study, unlike that
conducted by Gonzalez et al. (2006), there was no age limit and the patients did not have to be ambulatory.

Positive responders had lower pre-treatment scores for Vitality and Bodily pain than did negative responders. Though, this pattern was reversed after six month. It is important to identify responders and non-responders and as found here, negative responders as well, in order to offer treatment only to patients who will benefit from it. Patients who will not benefit from IVIG treatment should not receive it. Based on data from the present study, the SF-36 Vitality and Bodily pain variables may function as QOL outcome variables after IVIG treatment, and may serve as inclusion criteria for treatment.

Further studies are needed to narrow down the inclusion criteria. From the present study, it seems that PPS patients with higher fatigue and pain levels are more suited to receiving IVIG treatment.
5 GENERAL DISCUSSION

5.1 REFLECTIONS OF MAIN FINDINGS

Fatigue is a frequently occurring, subjectively experienced, and complex phenomenon, present, not only as a common symptom of PPS and other diseases, but is also present in healthy individuals after mental and physical effort. Fatigue can originate in the central or peripheral nervous system or a combination of both. It can be related to stress, disordered sleep, infection and inflammatory processes, muscle overuse, anxiety, pain, disordered breathing, or high altitude and can be experienced in various ways, for example as general, mental, physical or muscle fatigue.

The present studies found that fatigued PPS patients had no particular cognitive difficulties compared with non-fatigued patients. They also were younger and had a lower QOL compared with the non-fatigued patients. The variance in Vitality was mostly explained by General fatigue, which in turn was mostly explained by physical variables and inversely correlated with age, i.e., older patients had a less fatigue. These findings indicate that most fatigue in PPS could be described as physical and not mental. A follow-up of IVIG treatment revealed several combinations of response patterns, i.e., positive, non- and negative responders, with Vitality, Bodily pain and Physical functioning as the outcome variables, in which the positive responders were more fatigued and had more pain than the non responders before treatment. The younger age and the more severe QOL, sleep and pain symptoms in the fatigued PPS patients, in combination with the existence of several response patterns, indicate that there may be subgroups of PPS patients.

5.1.1 Do PPS patients experience cognitive difficulties?

In study I, PPS patients were divided into groups according to whether or not they felt generally fatigued, and their cognition was assessed using neuropsychological tests. Mental fatigue was provoked by cognitive load. The results indicated no differences in tests performance between the fatigued and non-fatigued PPS patients and that there were load effects. The conclusion of study I was that fatigue did not affect cognitive performance in PPS patients. Other studies (Bruno et al. 1993, 1994, 1995, 2000) have found indications that PPS patients may have subtle cognitive difficulties with attention and word finding. The results of study I may indicate that the tests used were not sensitive enough, and the inclusion of a healthy control group might have supplied additional information helping to resolve the issue. However, the results may also
indicate that general fatigue in these groups, as seen in study II, can mostly be defined as physical fatigue. It may be that physical fatigue does not affect cognition in the same way as mental fatigue does. Further studies including normal controls would be needed to conclude that cognitive disturbances are present in PPS patients.

5.1.2 Physical fatigue: the most prominent fatigue type in PPS?
In the large group of PPS patients examined in study II, the most prominent type of fatigue seemed to be physical fatigue. Variation in Vitality was explained by General fatigue which in turn was mainly explained by physical variables. It was therefore assumed that fatigue in PPS is primarily physical in nature. The findings of study II are confirmed by data from the studies by Trojan et al. (2004, 2009) and Schanke et al. (2001). However Bruno et al. (1994, 1995) suggested that brain-derived fatigue affects the subjective experience of fatigue in PPS. This assumption was based on abnormal CNS findings pertaining mainly to the reticular activating system (Bruno et al. 1994, 1995). The most severely fatigued group examined in study III, indeed suffered from mental fatigue, though even in this group, physical fatigue was primary and mental fatigue secondary. The results of the present studies, in accordance with data from other studies, point to that physical fatigue and not mental fatigue is the most prominent type of fatigue experienced by PPS patients.

5.1.3 Are there subgroups of fatigue in PPS?
PPS is in itself a complex phenomenon, just like fatigue. PPS patients all have their own histories and individual courses of polio: some suffer from persistent paralysis or weaknesses, while others recover to an almost normal level. The number of affected muscles also differs between polio patients. The results of study III indicate a significant difference between fatigued and non-fatigued PPS patients in terms of age, QOL variables, pain levels and sleep quality, giving rise to different subgroups on the basis of these variables. The question is whether these differences result from fatigue level or whether they can be explained by other factors, such as the increased pain seen in the fatigued group. Study IV found several patterns of response to IVIG. One group of patients displayed a positive response in at least two outcome variables, i.e., Vitality and Bodily pain, another group displayed a negative response in both. This would indicate that there are different subgroups in this respect as well. PPS is thus not homogenous but is a heterogeneous condition with different subgroups. It would be of interest to further characterize these subgroups to evaluate the role of biological or contextual influences in defining them.
5.1.4 Do all PPS patients benefit from IVIG treatment?
Several studies, i.e., Kaponides et al. (2006), Gonzalez et al. (2006), and Farbu et al. (2007), have identified a positive response to IVIG treatment in PPS patients, especially for the SF-36 subdomain of Vitality, and thus fatigue as well as pain. However, it was unclear whether all or just some patients experienced a positive response. The results of study IV indicate not only positive responses but the existence of several patterns of reaction to IVIG, i.e., positive, non-, and negative responders. Vitality was found to be a variable that may indicate a positive or negative treatment outcome. Effort should be made to further characterize responders, non-responders and negative responders, in order to offer treatment only to patients who will benefit from it and to avoid unnecessary treatment in patients who will not.

5.1.5 Clinical implications
Identifying the type of fatigue enables a more accurate focus in terms of treatment. The finding that fatigue is mostly physical in nature in PPS means that treatment and rehabilitation should focus on coping with and treatment of physical fatigue by saving energy, avoiding muscle disuse and overuse and physiotherapeutic interventions. However, in the most severely fatigued group, mental fatigue was present as well. It is important to lower the level of fatigue, since fatigue negatively affects QOL in general. Besides PPS related fatigue, PPS patients may, like everyone else, suffer from concomitant disorders having fatigue as a symptom and also be affected by “normal” fatigue: it is therefore important to thoroughly analyse the presented fatigue to be able to give the patient adequate care and therapy. Since the fatigued group examined in study III was younger, i.e., up to 65 years old, it is also important to into consider whether or not the patients’ work is physically demanding. More PPS patients in the fatigued group had contracted polio after 1956. The assumption was that this increased the possibility that they had contracted polio outside Sweden and might have a different contextual background – an aspect that may be important to take into consideration.

The results of the present studies indicate the existence of various subgroups of PPS patients and highlight the importance of using an individual approach when meeting a PPS patient. Taking contextual and emotional aspects into consideration may be important in helping these patients.
5.1.6 Future research

Several questions need to be answered concerning fatigue in PPS.

- To rule out cognitive dysfunction in PPS, a study including a group of healthy controls should be performed. The sample should be large enough and the presence of depression and other factors that can affect fatigue should be considered.

- The fatigued polio patients were younger than the non-fatigued patients examined in studies II and III. The question is why. It may be important to consider contextual factors including the work situation. It is also important to determine whether objective fatigue, defined as muscle weakness, increases and whether subjective fatigue decreases with increasing age.

- More of the fatigued patients had contracted polio after the introduction of polio vaccine in Sweden, i.e., after 1956. Do PPS patients who contracted polio before and after 1956 differ in terms of PPS related symptoms, QOL, mental health, family, and work situation?

- Connecting subjective QOL variables to biological parameters is another task for future research. Today we lack knowledge how the most common symptoms of PPS, i.e., muscle weakness, fatigue and pain, are related to inflammatory processes or other biomarkers.

- It is important to identify positive and negative responders before administering IVIG treatment. There may be factors, both in the background and contextual as well as the biological level that distinguish these different type of patients.

- PPS patients who had received more than one IVIG treatment were excluded from the sample. Finding out more about the effects of repeated IVIG treatment would be of interest. Would positive responders continue to be positive responders?

- Finding alternative treatment options, other than IVIG, for the negative and non-responders is another aim of future research.
6 SUMMARY AND CONCLUSIONS

6.1 CONCLUSIONS REGARDING MAIN FINDINGS

- There was no evidence that general fatigue or cognitive load affected cognitive functioning in PPS. No cognitive performance differences could be detected and systematic varying of test order did not cause significantly brain/mental fatigue.

- Vitality in PPS patients depends on physiological parameters. Mental fatigue is not a prominent predictor.

- Contrary to general belief, increasing vitality is correlated while pain is inversely correlated with increasing age in PPS patients.

- Fatigued PPS patients may be considered as a subgroup of PPS patients, characterized by significant lower age, more physical problems and lower QOL than non-fatigued PPS patients.

- In fatigued PPS patients mental fatigue was of relatively more importance for vitality than was physical fatigue.

- After IVIG treatment the total sample of PPS patients had significantly higher scores for the SF-36 sub-domains of Vitality, Bodily pain, Social functioning, Role-emotional and for MCS at the six-month follow-up than before treatment.

- The SF-36 sub-domains Vitality and Bodily pain may serve as outcome variables for IVIG treatment.

- PPS patients with low Vitality and Bodily pain scores may benefit from IVIG treatment while patients with higher scores may not.
7 ACKNOWLEDGEMENTS

The studies presented in this thesis were carried out at division of Rehabilitation Medicine, department of Clinical Sciences, Karolinska Institutet, Danderyd University Hospital and department of Rehabilitation Medicine, Danderyd University Hospital, Stockholm, Sweden.

I wish to express my sincere gratitude to everyone who in different ways have helped me into a realisation of this thesis. Especially I would like to thank:

All patients who participated in the studies. For being so generous with their time.

Kristian Borg, Professor, PhD, MD, my head tutor, for your generosity, enthusiasm and encouragement.

Åke Wahlin Professor, PhD, licensed psychologist, my assistant tutor for your ideas about design and statistics and for your guidance.

Marie-Lousie Schult, Occupational therapist, PhD, my mentor, for being positive, helpful and giving god advice.

Lisbeth Broman, Clinical laboratory scientist (CLS), Division of Rehabilitation Medicine, Karolinska Institutet, for your patients and all help with data, statistics, figures, tables and layout.

Britta Eklund, Administrator, division of Rehabilitation Medicine, Karolinska Institutet for your help with everything else.

Karola Ollas, Administrator, department of Rehabilitation Medicine, Danderyds University Hospital for your help.

Gullevi Bramert, Specialist nurse at the post-polio out clinic at Danderyd University Hospital for collecting data and administering questionnaires.

Karin Rudling, MD, former Head of Department of Rehabilitation Medicine, Danderyd University Hospital for providing me with everything necessary to complete my research.

Michael Ryd, MD, Head of Department of Rehabilitation Medicine, Danderyd University Hospital for listening to me and providing me with time.

Katharina Stibrant-Sunnerhagen, Professor, PhD, MD, co-author in study II and III for being encouraging, helpful and constructive.

Lars Werhagen PhD, MD, co-author in study IV, and very helpful with data collecting.

All people who used to be at Norrbacka. It was a nice time.

All my room mates during the years and everyone else at Building 39 at Danderyd University Hospital for providing me with a friendly environment and cheering me up.
All my former colleagues at Försäkringsmedicin/Hälsopartner, it was fun working with you. I learned a lot. You are all Great People!

A special thanks to all those not mentioned here and not forgotten, who have contributed in different ways during the years.

Eva, my friend since many years for being what you are.

Christina, my friend and colleague, for being encouraging and positive and always believing in my ability to do this.

Karl Erik Larsson, my friend who from the beginning planted the idea of doing research, you have always believed in me.

My cousin Paula and her children Markus and Nea, for connecting me with my roots.

Jo and Vroni, who introduced me to Schäfler, the best stress management mountain ever.

Nina, for providing me with a friendly and caring environment

Heinz, my partner in life, for always being there for me and being you.
8 REFERENCES


Borg K. Personal communication, 2010.


Cantor F. Central and peripheral fatigue: exemplified by multiple sclerosis and myasthenia gravis. PM R. 2010; 2: 399-405.


Katen KT, Beelen A, Nollet F. Overcoming barriers to work participation for patients with postpoliomyelitis syndrome. Disability and Rehabilitation. Accepted for publication June 2010; Early Online.


Kertesz A, Polk m, Carr T. Cognition and white matter changes on magnetic resonance imaging in dementia. Archives of Neurology. 1990; 47: 387-391.


