Treating fatigue in post-polio syndrome
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Chapter 1

General introduction
Poliomyelitis (derived from the Greek words ‘polio’ = grey and ‘myelon’ = marrow, indicating the spinal cord), often called polio or infantile paralysis, is a viral infection of the spinal cord or in sporadic cases the brain stem and bulbar region that can lead to the classic manifestation of flaccid paresis with intact sensation. Prior to 1900, poliomyelitis was endemic in the Western countries. However, as sanitation and hygiene in these countries improved, the transmission of poliovirus infections was delayed and infants were infected after the age of 12 months, when they were no longer protected by maternal antibodies. Epidemics of poliomyelitis appeared and polio became a global disease with annual outbreaks beginning in the early 20th century. At its peak in the 1940s and 1950s, just before the introduction of routine vaccination, the poliovirus paralyzed or killed over half a million children and adults worldwide every year, and the total number of polio survivors now is roughly estimated at 10 to 20 million.1

The tremendous efforts of the Global Polio Eradication Initiative (GPEI) of the World Health Organization (WHO) have been very successful in reducing the number of polio cases worldwide. In fact, wild poliovirus transmission is now at the lowest level, with fewer cases reported from fewer areas of fewer countries than ever before. For 2015, up till December 31, 74 wild poliovirus cases have been reported from two endemic countries (Pakistan and Afghanistan), compared to 316 cases from nine countries (3 endemic, 6 with regional outbreaks) during the same period in 2014.2 However, until poliovirus transmission is interrupted in the remaining two endemic countries, all countries remain at risk of importation of polio. Eradicating polio for good requires not only the elimination of wild poliovirus, but also of circulating vaccine-derived poliovirus (cVDPV) which is a very rare, infectious virus mutated from the weakened strain of poliovirus in the oral polio vaccine, that mainly occurs when oral vaccination is incomplete. After wild poliovirus transmission has been stopped, oral polio vaccination can be replaced by inactivated polio vaccine which cannot cause cVDPV.3 The most important challenges for global polio eradication now are the spread from international travel4 and the political factors such as weak health systems, public mistrust, political instability, and other conflicts that hinder mass vaccination campaigns to achieve high immunization rates.5 In May 2013, the GPEI set a new deadline for polio eradication for the year 2018.5

Acute polio

Poliomyelitis is spread from person to person through the faecal-oral route or in some cases by contaminated water or food. In most cases the infection passes by unnoticed without symptoms or gives mild influenza-like symptoms. However, in about 0.5 percent of all infections, the poliovirus causes a selective destruction of the anterior horn cells of the spinal cord and the motor neurons of the lower brain stem.6 This results in a flaccid, asymmetrically distributed
paresis or paralysis of a varying number of muscle groups. The death-to-case ratio for paralytic polio is approximately two to five percent among children and 15 to 30 percent for adults, which increases up to 25 to 75 percent with bulbar involvement. After the acute phase, usually there is partial and sometimes even complete recovery of muscle function from the self-terminating disease which may take 2-3 years. Mechanisms contributing to the recovery of the muscle function include the survival of motor neurons, reinnervation of denervated muscle fibers by collateral sprouting, and muscle fiber hypertrophy. The period of recovery is followed by a period of stable neurologic functioning of about 15 years or more, leaving individuals with a wide variety of sequelae, which may vary from mild muscle weakness in one extremity to severe paresis or paralysis of upper and lower extremities, trunk and bulbar muscles. Mostly, this is accompanied by dysplastic development of extremities with bony deformities, and muscle and joint contractures during growth.

The post-polio syndrome

Survivors of paralytic poliomyelitis may develop increased or new neuromuscular symptoms after the period of stable neurologic functioning, known as post-polio syndrome (PPS). These symptoms may include new or progressive muscle weakness, abnormal muscle fatigability, generalized fatigue, muscle atrophy, muscle and joint pain, muscle cramps, and cold intolerance. Less commonly, symptoms attributed to PPS include breathing and swallowing difficulties. The exact prevalence of PPS is difficult to establish and depends on the criteria applied and population studied, but is estimated to affect approximately 60% of all patients with previous paralytic polio.

The diagnostic criteria for PPS have changed over time. The criteria published by March of Dimes in 2001 are currently accepted for the diagnosis of PPS (Table 1). ‘Late-onset sequelae of polio’ or ‘late effects of polio’ are broader terms used to describe new symptoms polio survivors may experience, including medical conditions more distantly related to the polio, such as osteoarthritis or entrapment neuropathies. The pathogenesis of PPS is still unclear and is probably multifactorial. The most widely accepted assumption is that the motor units, which are enlarged due to collateral sprouting in the early recovery phase, do not remain stable throughout life. There is distal degeneration of axons, possibly because of persistent high metabolic stress. The initial balance between denervation and re-innervation of muscle fibers becomes disrupted and when denervation predominates, progressive muscle weakness occurs. Findings of single atrophic muscle fibers in muscle biopsy studies and spontaneous activity of motor unit action potentials on electromyography support this hypothesis. A recent longitudinal study in patients with PPS also corroborates the notion that enlarged motor units cannot
be sustained indefinitely by demonstrating that motor unit size declined over time, which was greatest in the muscles with the fewest remaining units, and that the rate of denervation was related to the rate of strength decline.21

Table 1. Diagnostic criteria for post-polio syndrome.

1. Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness, and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).
2. A period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years of more) of stable neurologic function.
3. Gradual or sudden onset of progressive and persistent muscle weakness or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain.
4. Symptoms persist for at least 1 year.
5. Exclusion of other neurologic, medical, and orthopedic problems as causes of symptoms.

Published by March of Dimes in 2001.

Other supposed explanations for the pathogenesis of PPS include virus persistence22 and an inflammatory process, based on the finding of raised concentrations of pro-inflammatory cytokines in the cerebrospinal fluid.23 Factors that may contribute to the symptoms of PPS are neuromuscular transmission defects24 and an impaired ability to activate muscles.25,26 PPS is considered a slowly progressive condition. From longitudinal studies with a follow-up duration ranging from five to ten years, the annual rate of decline in muscle strength is estimated to vary from 1.5 to 2%.21,27,28 This decline in muscle strength leads to a decline in functioning as the reduced muscle capacity falls short to meet the demands of daily physical activities.29

Fatigue in post-polio syndrome

Is has been shown that the decline in functioning not only results from a decline in muscle strength, but is also caused by fatigue.30 In fact, fatigue is one of the most common complaints of PPS.12,31,32 In a study on disability and health problems in 76 Dutch patients with PPS, 78% of the subjects selected fatigue as their main problem, exceeding difficulties in walking outdoors (45%), climbing stairs (41%) and pain (39%).32 Compared to healthy individuals, patients with PPS experience much higher levels of fatigue,34,35 and besides a decline in functioning, symptoms of fatigue are also associated with reduced health-related quality of life (HRQoL).30,36

Fatigue is generally described as a complex multidimensional phenomenon, and there is no
widely accepted definition for fatigue. Patients with PPS describe their fatigue as tiredness or lack of energy that increases with physical activity and decreases with rest.\textsuperscript{37} In this thesis, when we report on fatigue, we mean experienced fatigue, which in other neuromuscular diseases is sometimes distinguished from physiological fatigue (defined as the loss of voluntary force-producing capacity during exercise).\textsuperscript{38-40}

The etiology of fatigue in PPS is poorly understood and it may be presumed that multiple pathways lead to the causation and persistence of this fatigue. Biological factors associated with fatigue in PPS include poliovirus-induced lesions in the brain,\textsuperscript{41} an inflammatory process,\textsuperscript{13} respiratory dysfunction,\textsuperscript{42} pain,\textsuperscript{32,44} and co-morbidities.\textsuperscript{35} A physical factor that is associated with fatigue in PPS is the persistently reduced muscle function.\textsuperscript{42} In addition to these biological and physical factors, psychological factors are also known to be associated with fatigue in PPS, and include dysfunctional cognitions and behavior, depression,\textsuperscript{42,45,46} anxiety\textsuperscript{45,46} and psychological distress.\textsuperscript{42} However, the above-mentioned factors of fatigue have been investigated in different studies with cross-sectional designs and therefore the interaction, temporal sequence and causal effects of these factors are not fully understood.

**Treatment for fatigue in post-polio syndrome**

Due to the multifactorial pathogenesis of PPS and symptoms of fatigue in PPS, a wide variety of pharmacological and non-pharmacological interventions for its treatment have been studied.\textsuperscript{47,48} These interventions vary in terms of their respective points of action and targeted effects. In 2006 an expert task force, appointed by the scientific committee of the European Federation of Neurological Societies (EFNS), evaluated the existing evidence for the effectiveness of therapeutic interventions and provided a clinical guideline for the management of PPS.\textsuperscript{49} This guideline was updated in 2011.\textsuperscript{11} However, no systematic reviews using transparent methods for summarizing research evidence and providing a quantitative assessment of the overall magnitude of treatment effects for interventions in PPS are available. Such an analysis is needed to further elucidate the effectiveness of different treatment modalities in PPS and to better direct decisions about future research for treating fatigue in PPS.

In current clinical practice, rehabilitation management is considered the mainstay of treatment. Rehabilitation is aimed at reaching a functional balance by increasing capacities and reducing demands, and several different rehabilitation approaches may be applied such as strength training, aerobic exercise therapy, assistive devices, orthoses, lifestyle changes, psychological support, respiratory muscle training, speech and swallowing therapy, and sometimes ventilator support.\textsuperscript{11,47}
Exercise therapy for alleviating fatigue in post-polio syndrome

Exercise therapy (ET) has been proven an effective intervention for alleviating fatigue in healthy individuals and in various medical conditions. The rationale for ET as a treatment for fatigue is based on the assumption that it can break the cycle of fatigue leading to physical inactivity and, consequently, deconditioning (i.e. reduction of a person’s physical capacity). This reduction in physical capacity results in an increased effort to perform daily activities, which, in turn, leads to more fatigue. The direct effect of ET may be improvement of physical capacity, though it may possibly also exert its effects on fatigue through other pathways such as improving mood and changing cognitions.

Many patients with PPS show low levels of physical activity, most probably resulting from muscle weakness and other symptoms of PPS. Although, previously, patients with PPS were advised to avoid intensive exercise as this could worsen muscle weakness and fatigue, later on, physically active PPS patients were found to have less symptoms of fatigue than sedentary patients. A systematic review on ET for neuromuscular diseases included ten studies on patients with PPS, five of which demonstrated positive effects of ET on muscle strength and cardiorespiratory fitness and no adverse effects. A more recent study on a home- and hospital-based aerobic exercise training in PPS also showed improvement on fatigue and HRQoL. However, a comparison with a control group was not made and long-term effectiveness was not evaluated. Therefore, further research is needed to draw definite conclusions on the effectiveness of ET in reducing fatigue in PPS.

CBT for alleviating fatigue in post-polio syndrome

Cognitive behavioral therapy (CBT) has been proven another effective treatment strategy for reducing fatigue in various patient populations. The fundamental aim of CBT is to identify dysfunctional cognitions derived from long-standing negative beliefs and assumptions. The CBT model proposes that by challenging the meaning of these cognitions and eliciting more realistic cognitions, emotions and behaviors can be changed. There is growing evidence that not only biological, physical and general psychological factors are related to fatigue in different patient populations, but also cognitive and behavioral factors. These cognitive-behavioral factors are known to play a significant role in perpetuating or worsening fatigue in chronic fatigue syndrome and fatigued cancer survivors, as well as in multiple sclerosis, which, alike PPS, is a
chronic condition with muscle weakness as a common symptom. Some of these cognitive-behavioral factors are also associated with fatigue in PPS, including a reduced self-efficacy, type-A behavior, reduced physical activity and reduced sleep quality. Therefore, a CBT-intervention aimed at changing these cognitive-behavioral factors in PPS seems plausible.

Evidence for the effectiveness of CBT in PPS is currently limited to an uncontrolled study of cognitive behavioral strategies incorporated in a multidisciplinary rehabilitation program. Although a reduction in fatigue was found, it is unclear whether this can be ascribed to the cognitive behavioral components of the intervention. Therefore, also for CBT, more research is required to gain insight in the effectiveness on alleviating fatigue in PPS.

Aims of this thesis

Despite the high burden of fatigue in PPS and the impact it has on functioning, it is an as yet poorly understood symptom when it comes to its etiology, the course over time and its treatment. The general aim of this thesis is to expand the knowledge on treatment of fatigue in PPS. The first part of this thesis concerns research aimed at measuring fatigue, gaining insight in the severity, course, and factors related to fatigue, and reviewing the existing evidence on the effectiveness of different treatment modalities for PPS. The second part of this thesis concerns research aimed at reducing fatigue in PPS.

Outline of this thesis

**Chapter 2** describes a study in which we compared the content of two questionnaires measuring fatigue in PPS (the Fatigue Severity Scale and the subscale “subjective experience of fatigue” of the Checklist Individual Strength). This is done by means of linking concepts contained in the questionnaire items to the International Classification of Functioning, Disability and Health (ICF), using standardized linking rules. In addition, the reliability (internal consistency, test-retest reliability and measurement error) of these questionnaires in polio survivors is investigated.

**Chapter 3** describes the severity and five-year course of fatigue in patients with late-onset sequelae of poliomyelitis (LOSP). Furthermore, biological, physical, general psychological and cognitive-behavioral factors of fatigue are investigated. Results are based on data collected within ‘the Comorbidity and Aging effects in Rehabilitation Patients on Activities study’ (CARPA). The CARPA-study is a prospective and ongoing follow-up study investigating the course of functioning in patients with LOSP.
Chapter 4 presents a Cochrane systematic review on the effectiveness of any pharmacological or non-pharmacological treatment for PPS compared to placebo, usual care or no treatment on self-perceived activity limitations, muscle strength, muscle endurance, fatigue, pain and adverse events.

In Chapter 5, the design of a three-arm multicenter, single-blinded, randomized controlled trial, the FACTS-2-PPS study, is described. FACTS-2-PPS stands for Fitness And Cognitive behaviourial TherapieS for Fatigue and ACTivitieS in PPS. The study aims to investigate the efficacy of ET and CBT on reducing fatigue, and improving daily activities and HRQoL in patients with PPS. This study is part of the FACTS-2-NMD study program (Fitness And Cognitive behavioral Therapy for Fatigue and ACTivitieS in NeuroMuscular Diseases). Within this study program, two other randomized controlled trials with a similar approach in intervention and outcome measures are being conducted in patients with amyotrophic lateral sclerosis (ALS) and facioscapulo-humeral muscular dystrophy (FSHD).

Chapter 6 presents the results of the FACTS-2-PPS trial. In two successive chapters we explore possible explanations for the found lack of efficacy of the two interventions. In Chapter 7 this was done for the ET intervention, where a precise quantification of the actually realized training dose and the effects on muscle endurance are investigated. In Chapter 8 this was done for the CBT intervention, by investigating the role of the assumed fatigue related cognitions (sense of control over fatigue; catastrophizing; acceptance of the disease; focusing on fatigue symptoms; and perceived social support) in PPS.

To conclude, Chapter 9 is the general discussion of this thesis, in which the results obtained in the studies described in Chapter 2 to 8 are critically discussed and clinical implications and ideas for future research are presented.
References


Chapter 1  General introduction

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