Prolonged Unexplained Fatigue in Paediatrics.

Robert Jan Bakker

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Prolonged unexplained fatigue in Paediatrics.

Aanhoudende onverklaarde moeheid in de kindergeneeskunde

(met een samenvatting in het Nederlands)

Oanhâldende net te ferklearjen wurgens yn de bernegenêskunde

(mei in gearfetting yn it Frysk)

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geboren op 3 februari 1944 te Amsterdam

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Better let dan net

Ter nagedachtenis aan mijn ouders

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List of abbreviations

AOM	Aanhoudende Onverklaarde Moeheid
CBT	Cognitive Behavioural Treatment
CDC	Centres for Disease Control and Prevention
CFS	Chronic Fatigue Syndrome
CHQ-CF	Child Health Questionnaire-Child Form
CI	Confidence Interval
CIS-20	Checklist Individual Strength (20 items)
CSI	Children’s Somatization Inventory
CVS	Chronisch Vermoeidheid Syndroom
GET	Graded Exercise treatment
GP	General Practitioner
ME	Myalgic encephalomyelitis
NICE	National Institute for Clinical Excellence
PUF	Prolonged Unexplained Fatigue
RCPCH	Royal College of Paediatrics and Child Health

Chapter 1

General introduction

Fatigue

Fatigue is a common subjective experience of a common physiologic phenomenon as the result of mental or physical exertion. However, it can be a symptom of illnesses such as infections, metabolic diseases, malignancies and major depression.[1-5] Accordingly it can occur without preceding exercise and without associations with known illnesses or diseases: the fatigue is a disease in itself.

Fatigue is a universally experienced but aetiologically not well understood symptom. There is no clear universal definition of fatigue in the literature.[6,7] Fatigue is expressed in related concepts such as 'overwhelmingly tired', 'exhausted', 'weakness', 'lassitude', 'feeble lethargy', 'lack of energy', 'wrung out' and 'mentally tired'.[8,9] Linguistic differences in the description of fatigue/tiredness between healthy and ill individuals revealed different perceptions of the phenomenon.[10] The different descriptions represent varying degrees of the intensity and of the impact it has on functional ability, and highlight fatigue as idiosyncratic and highly personal.[11] For the communication between the practitioner and the patient it is essential to know from each other what they mean when they speak about fatigue. This is also true for the communication between practitioners and researchers. The different descriptions of fatigue may be a problem of semantics, but also an expression of different types of fatigue. Unless professionals are able to interpret the many meanings and metaphors, research findings will be inconsistent and interventions potentially ineffective.[11] For research purposes an operational definition is a conditio sine qua non.

Definitions of fatigue

The Oxford English Dictionary (1989) definition refers to fatigue as meaning ‘Lassitude or weariness resulting from bodily or mental exertion.’ It stems from the Latin Fatis, which means 'yawning' (Dutch: *afmatting)* and Fatigare (Fatis Agere) *(* Dutch: *vermoeien).* The PubMed (a service of the U.S. National Library of Medicine and the National Institutes of Health) has a more extensive definition: ‘Fatigue is a state of weariness following a period of exertion, mental or physical, characterized by decreased capacity for work and reduced efficiency to respond to stimuli.’ Furthermore, some specific sub-definitions are given: ‘Muscle fatigue is a state arrived at through prolonged and strong contraction of a muscle; mental fatigue is a state arising in consequence of mental effort and auditory fatigue is a loss of sensitivity to sounds as a result of auditory stimulation.'

Acute fatigue has been defined as being equivalent to an increased 'sense of effort' while performing a given task. It is a subjective feeling that might become so intense that one is forced to stop or reduce the exercise, meaning one has reached the point of exhaustion. Acute fatigue and exhaustion are normal exercise-associated physiological phenomenona. They have protective functions and are transient, relieved by rest (sleep), drinking and eating.[12]

Chronic fatigue is not transient but pervasive or episodic. It persists over time and is not relieved by rest or nourishment. For chronic fatigue PubMed has no other definition than the description of the fatigue of the Chronic Fatigue Syndrome, characterized by persistent or recurrent fatigue, diffuse musculoskeletal pain, sleep disturbances and subjective cognitive impairment of 6 months duration or longer. Symptoms are not caused by ongoing exertion, are not relieved by rest, and result in a substantial reduction of previous levels of occupational, educational, social or personal activities. Minor alterations of immune, neuroendocrine and autonomic function may be associated with this syndrome. There is considerable overlap between this condition and fibromyalgia.

Holmes et al established in 1988 the first operational definition of Chronic Fatigue Syndrome. This definition has been revised by the Centres of Disease Control and Prevention (CDC) in 1994.[13,14] In the revision, all physical signs and a requirement for 50% reduction in activity were dropped from the inclusion criteria, the number of required symptoms was decreased, and some psychiatric disorders were dropped as a basis for exclusion. The CDC defined Chronic Fatigue Syndrome as an illness characterized by more than 6 months of disabling fatigue associated with 4 or more of the following symptoms: impaired memory or concentration, sore throat, tender cervical-axillary lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshed sleep and post-exertion malaise.[14] The importance of these associated symptoms in CFS and the question whether they contribute to defining a homogenous group of individuals with disabling fatigue has been increasingly questioned.[15,16] CFS is a diagnosis by exclusion of any other illness or disease.

Despite all improvements of the first Holmes definition with clear but difficult to objectify criteria, the degree of the fatigue will remain subjective in a particular case. Many patients fail to meet the criteria for CFS, but have serious complaints of fatigue and substantial associated impairment.[17] Particularly for children and adolescents the criterion of 6 months duration is very long, and with respect to the educational and psychological development of youngsters for the Royal College of Paediatrics and Child Health a reason to suggest reducing the period of disabling fatigue from 6 to 3 months for children and adolescents.[18]

In literature, different adjectives are used for non acute fatigue outside the realm of CFS criteria: prolonged fatigue,[19,20] chronic fatigue,[21] disabling fatigue,[22] unexplained fatigue,[23] and idiopathic chronic fatigue syndrome.[24] Using different adjectives within the same group of patients makes comparisons between different research reports difficult. Furthermore, the use of the adjective Chronic in non CFS cases can be deluding and may have negative connotations such as "lasting the rest of your life" and offers by that little hope for recovery. In paediatric literature uncertainty exists about how to define disabling fatigue in children and adolescents.[25] A number of authors have raised the concern that the current criteria for CFS do not fit in with children and adolescents.[26-28] For children and adolescents it must be noted that their activity level, school attendance, and social involvement are often under control of their parents. Functional impairment may be influenced for that reason as much by the parent's behaviour as by the illness itself. Reviews on disabling fatigue in this age group highlight the lack of research in comparison to adults.[18,29] Given the current discussion about the role of associated symptoms in CFS in adults, and the lack of empirical testing of the appropriateness of the adult CFS criteria for children and adolescents, there is a need to examine how the clinical and demographic features of children and adolescents differ in those who fulfil CFS criteria and those who fulfil broader criteria for disabling fatigue.[25] The latter may represent an important group of individuals who require treatment and support. Fowler found the degree of impairment (in terms of interference with usual activities, family and peer relationships, school absence and school work) to be similar in children who fulfilled the adult CFS criteria (6 months plus) or the child criteria (3 months plus) and in children with disabling fatigue (3 months plus) without any more criteria.[25] Although this does not prove that there are no differences between individuals in these groups, it indicates that it may be appropriate to consider a broader definition of disabling fatigue in children and adolescents for clinical and research purposes.

In our research on disabling fatigue in children and adolescents we will use the term: Prolonged Unexplained Fatigue (PUF): A subjective state of disabling weariness not resulting from ongoing bodily or mental exertion and not explained by any known somatic or mental disease in such an intensity and duration that the patient seeks medical help. A little exercise or even the feeling of having to exercise can lead already to an increased 'sense of effort'. It feels like a lack of energy and does not fade away by rest, sleep or nourishment. PUF is neither a distinct nosological disorder nor a discrete diagnostic entity. It is based on subjective symptoms and disability.

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History of Chronic Fatigue

After that the New York's neurologist Beard reported in 1869 a new disorder 'neurasthenia', which was characterized by fatigue related to the special stress of the modern civilisation of those days,[1] specialised clinics opened up in whole Europe. In France, Charcot wrote about "La maladie à la mode" or "La maladie americain," [2] and suggested that overburdening of the nervous system might result in exhaustion. Neurasthenia started as a disease of people from the "higher class", but when after some time, also normal "working people" proved to have the same complaints, the attention disappeared in the western medical world,[3] contrary to the Far East, where the concept still exists within the Yin Yang philosophy.[4] Half way the last century after the first publication concerning the outbreak in the Royal Free Hospital,[5] more outbreaks of fatigue with neurological symptoms in western countries were published with different names: myalgic encephalomyelitis (ME), Iceland disease and epidemic neuromyasthenia.[6,7] From the eighties on, after an article of Straus et al,[8] the attention grew enormously, with new specialised Chronic Fatigue Syndrome clinics and with research, based on the ME/CFS definitions, first only in adults and later in youth.[9] The history repeated itself.

One spoke about a modish disease again and the recognition as a real status is still under discussion.[10] Because of conflicts between patients and insurance companies, Chronic Fatigue Syndrome has been certified by court in North America,[11] and is the only legally supported medical diagnosis. In the Netherlands, researchers and clinicians prefer the describing neutral diagnosis CFS, while members of patients associations mostly use the name ME.

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Pathophysiology

Exercise-induced fatigue is the perception that physiological bounds are nearing. The central nervous system is informed by messengers, such as cytokines and (neuro) hormones, and regulates the physical and mental activities. When fatigue is observed one can stop or continue the activity, and subsequently the fatigue will be resolved by rest, food and drinks. When fatigue is a symptom of disease, the same dysbalancing mechanisms are involved, with the same considerations to rest or to start activities. This symptomatic fatigue will be resolved when the dysbalance is corrected by convalescence of the disease.[1-4]

The pathophysiology of chronic fatigue is still hardly understood. It is reasonable to suppose that the same mechanisms are involved as in acute fatigue, but many other pathophysiologic mechanisms have been postulated and the evidence of discrete abnormalities in the different body systems is suggestive for a multi factorial illness.

The hypothesis of the 'ongoing disturbed homeostasis' provides a comprehensive basis. Already in 1865 Claude Bernard wrote his concept of homeostasis as the processes whereby the internal environment of an organism tends to remain balanced and stable.[5] An organism is living with continuously changing processes in a stable equilibrium. In the balance status the different links of the different systems of an organism fluctuate with limited amplitudes around an individual setpoint.[6] These set points themselves also can fluctuate during the day (circadian), during the year (circannual), during the menstrual cycle and during the life time.[7] The homeostatic regulation is based on ‘feed back and feed forward’ principles in a network of different mutually related systems:[8,9] The endocrine system with a central place for the hypothalamic-pituitary-adrenal axis (HPA-axis),[10-12] sympatic nervous system,[13-14] dopaminerg system,[13,15] cortical and subcortical structures of the nervous system,[16,17] limbic system,[18,19] immune cells and cytokines.[1-4,20] Very different factors such as infections, physical or psychological traumas and mental threat can disturb the homeostasis of the network of related systems through different points of action. These factors are called stressors.

There are different definitions of stress based on the 3 different aspects: Stimulus, Response and Dynamics.[21] Each of them contributes to a better understanding. The Stimulus aspect limits itself to external stressors and reckons with its nature to cumulate different stressors. The Response aspect concerns the reaction in physiological terms as changes in the HPA-axis, heart rate, blood pressure and so on. The Dynamic aspect contains individual features, gender, living circumstances, cognitive factors, social interactions, life history and so on.[21-24] The dynamic process of stress can be defined as the way how one observes problems and interprets them, how one reacts and tries to cope and the price to pay for that all.[25] It is the way a person responds to his environment. There are great differences between individuals in stress perception and coping.[26] The stress reaction has the aim to enable someone to withstand an (imminent) disturbance of his homeostasis, and has to be controlled in the same time. The different, by stress responses activated, links in the psycho-neuro-immuno-endocrinal network must return to their status of rest to restore the homeostasis. Fatigue is, in that view, a symptom of a disturbed homeostasis, and will stay on as long as the physiological rest state has not been reinstalled. Chronic Fatigue Syndrome may be considered as a symptom-complex of a 'chronic disturbed homeostasis'. While the cause of the disturbance does not exist anymore, the rest state has not been reached. The hypothesis is that predisposing and causal factors as well as perpetuating factors are involved in chronic fatigue.

A disproportional balance between stressors and the physiological capacity of the homeostasis may result in disorganization of the mutually related systems with changed set-points and sensitivity of receptors.[27-28] In that case the stable homeostasis is at risk to be replaced by a status in which stability is obtained by changing the biological variables. This is an unstable equilibrium called ’allostasis’,[29-30] and the pathological mechanism responsible for stress related complaints.[31] Other diseases related with chronic fatigue are very similar to CFS, although the aetiology is much different.

Exercise-related fatigue is a physiological phenomenon in which the exercise will be the stressor and the cause of fatigue. It is the warning signal to stop exercising to prevent harm, and it will be relieved by rest.[32] Going on with activities beyond physiological bounds may lead by the perpetuing stress reactions to adaptation syndromes,[33-35] such as ‘Burnout syndrome’,[36-38] and ‘Overtraining syndrome’.[39.40]

Disease and treatment related fatigue is a part of ’sickness behaviour’[1-4] and will be relieved after convalescence, but will remain one of the most common complaints in chronic diseases such as rheumatoid arthritis[41] and Crohn’s disease.[42]

Cancer-related fatigue is one of the most distressing side-effects during cancer treatment, [43] and can persist for years after curative treatment in a rate comparable to CFS.[44] There is much speculation about the mechanisms responsible for cancer-related fatigue.[45] The malignancy itself and/or treatment disturb the homeostasis, while other factors contribute to the persistence; for example depression, psychological distress, physical distress, tendency to develop catastrophizing thoughts in response to fatigue, functional disability, and quality of sleep[44-47] Posttraumatic stress symptoms (intrusive thoughts, physiologic arousal and avoidance) have been documented in childhood cancer survivors as well in their parents many years later.[48-51]

In exercise- as well disease- and treatment related fatigue, fatigue occurs as a signal of (imminent) derangement of the inner balance and will be relieved only after its re-establishment. It is an urgent request for rest and getting a save place for recovering. In that view it is a response that has been anchored in an evolutionary way.

In Prolonged Unexplained Fatigue and Chronic Fatigue Syndrome, fatigue seems to have lost this evolutionary function. Some youngsters are more vulnerable for this development than others by genetic predisposition,[52] lack of support or family dynamics.[53]

The model of predisposing, precipitating and perpetuating factors offers an global insight into the pathophysiology of this ‘useless and fruitless’ kind of fatigue and serves as a point of departure for treatment.

Factors involved in Prolonged Unexplained Fatigue in Childhood

	Predisposing	Precipitating	Perpetuating
Biological	Genetic vulnerability	Disease or somatic trauma	Neuro-immuno-endocrinal pathophysiology
Psychological	Vulnerable personality	Stress or psycho trauma Life events	Depression, anxiety, unhelpful beliefs, fearful avoidance of activity catastrophizing
Social	Lack of support, family dynamics	Social or school stress	Reinforcement of unhelpful beliefs, social or school stress

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Epidemiology

Complaints of fatigue, listlessness and tiredness are common subjective experiences in the general population. The difficulties with definitions have affected the results of epidemiological studies. Large community surveys indicate that up to half of the populations experience fatigue of limited duration.[1,2] So, fatigue seems to belong to experiences of normal life. It is estimated that approximately 9% of British people experience fatigue of more than six months' duration at any time.[3] After respiratory symptoms, complaints of fatigue are the most common physical symptoms in the general practice: [4] in 11 to 33 % of the first visits.[5-9] In 8,5 % these complaints interfered with the daily lives for at least six months whereas no apparent medical cause was found.[5] In a review by Prins et al[10] based on the 1994 case definition of the Centres of Disease Control and Prevention, two community based studies were reported with prevalences of CFS among adults of 0,23 % and 0,42 % in the US.[11,12] One prospective primary-care based study in the UK reported a prevalence of 0,50 %.[8] One has to realise that patients, who fulfil the CDC criteria, are at the end of a fatigue spectrum that runs from not fatigued at all to debilitating severe fatigue for a long time.[13,14] Most people with complaints of fatigue can not be diagnosed as patients with CFS and many of them will never visit a practitioner for help. The incidence and prevalence of this group are much higher. The strong CDC criteria for CFS have been drawn up for scientific research reasons, but in general practice the usefulness of distinguishing patients with prolonged unexplained fatigue from those with CFS is a point of debate,[15] especially in pediatrics.[16]

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Children and adolescents

The last decades paediatricians witness an increase in the incidence and prevalence of severe fatigue complaints in children, often leading to very restricted physical and social life.[1] For 2 % of school children attending general paediatric clinics, fatigue is the major presenting problem and for 11% a background problem.[2] Estimates of the prevalence in children vary widely according to case definition and methodology, but they suggest that the prevalence is lower than among adults.[3] In a cross sectional study in the UK Chalder et al found that symptomatic fatigue in 5-15 years olds is common, but prolonged debilitating fatigue and CFS are relatively rare.[4] The fatigue may fluctuate in intensity, [5] exacerbate by exercise and have brief episodes of remission.[6,7] With 0,85 % the prevalence of CFS in childhood is lower than found in equivalent surveys in adults. Risk factors were older age and anxiety disorders.[4] CFS-like illness prevalence has been estimated at 4.4 % in a US adolescent population,[8] and Farmer et al found in two population-based twin registers from 8-17 years that the prevalence of fatiguing illness lasting 3 or more months was 2,34 % and the prevalence of 6 or more months of fatigue was 1,29 % with a mean age of onset of about 12 years.[9] Other studies show a higher mean age of onset of 14.3 [10] and 13 years.[11] These studies confirm that chronic fatigue is rare in children under 10 years of age, but those aged over 11 show a change to a similar prevalence, symptom profile and gender distribution (girls outnumber boys 3:1) as adults do.

In a Dutch survey among an adolescent school-based population 20,5 % of the girls and 6,5% of the boys had complaints of severe fatigue. 80% of these girls and 61,5% of these boys reported fatigue lasting 1 month or more.[12] For this survey no referral or treatment-seeking bias existed. The prevalence of the Chronic Fatigue Syndrome according the CDC definition in children and adolescents in the Netherlands is estimated to be 10 - 20 per 100.000 inhabitants.[13]

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The impact of disabling fatigue on children and adolescents

In its severe form fatigue is often, but not always triggered by infectious illness episodes and commonly associated with mood disorders. Parents are heavily emotionally involved in the problems of their child and many view the condition as a medical disorder.[1] It is an important clinical problem associated with severe functional impairment and has an impact upon the child's educational and social development. It causes impaired relationships with family and friends, reduces participation in leisure activities, [2-4] and is the main illness-related reason for long-term school absenteeism.[5]

Most studies on childhood chronic fatigue have been on children with CFS attending specialist paediatric clinics. Not much is known about the condition as it presents itself in other medical services. Children and adolescents, who do not fulfil the narrow CDC definition of CFS, but suffer from disabling fatigue, severe enough to seek medical care, show comparable substantial impairment. Their absence from school is comparable and there is no significant difference with CFS patients in gender ratio, the average age of onset or the rate of co-morbidity with depression.[6,7] They differ in the first place in the duration of the complaints. Psychopathology and personality problems are common in children and adolescents with severe forms of CFS and cannot be explained strictly through the experience of chronic physical illness.[8] Severe fatigue states can cause serious and long-lasting handicap. A systemic review reported that two third of youngsters with CFS made a full recovery, but our follow up study in a university hospital setting showed a worse prognosis[9] Half of the patients were still severely fatigued, had impaired physical functioning, experienced substantial bodily pain, and was in bad health 3.2 years after initial assessment.[10]

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Therapy

“Chronic Fatigue is a condition, which, for a number of reasons, has caused more polarisation of views and more conflict between patients and their doctors than perhaps any other illness” (Royal College of Paediatrics and Child Health, 2004).

The severe functional impairment and the inexplicability of the fatigue in PUF and CFS affect emotional and cognitive processes, while emotional and cognitive processes may enhance impairment. Concerning the therapy it is useful to make a distinction between precipitating and perpetuating factors. When thorough physical examinations and laboratory tests have not revealed the cause of fatigue, further examinations will be unnecessary and even harmful for the patient. Diagnostic delay can cause anxiety in the patient and family. As long as the lack of understanding is a stressor it will affect emotions and cognitive processes. The assumption is that the trigger of the onset of fatigue has passed, but the homeostasis of the psycho-neuro-immuno-endocrine network has not been returned. Perpetuating factors may be responsible for the persistence of complaints; for example, fear for underlying disease, sleep quality, physical (in)activity, cognitions related to fatigue and the use of catastrophizing as coping strategy.[1] Adolescents with CFS attribute their health more to external factors.[2] The cognitive behavioural models of CFS emphasise the importance of patients’ illness perceptions in perpetuating this disorder.[3] Cognitive behaviour therapy has been based on these principles. Several randomised controlled trials have shown that cognitive behaviour therapy is effective in adults with CFS[4,5] and adolescents.[6] A cognitive behaviour therapy based on gradually increasing activity and challenging perpetuating beliefs and concerns helps adolescents with CFS.[7] This combined therapy is the only proved and currently the most effective therapy in adult and adolescent CFS-patients[8] Because there is no essential difference in the severity of fatigue between CFS and PUF and many patients with PUF by definition will become in time CFS patients, this therapy might be effective for them as well.

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Objective and outline of the study

Most patients in general paediatrics, referred by general practitioners because of ongoing fatigue, do not fulfil the CDC criteria for Chronic Fatigue Syndrome, but have nonetheless severe disabilities. Not many studies have been carried out particularly on these fatigued children and adolescents. In the absence of any explanation by means of physical signs or abnormalities in laboratory test results, these patients create a main problem for practitioners. For that reason, we have confined our self in this study in general paediatrics to children and adolescents from age 8 till 18 years old with Prolonged Unexplained Fatigue (PUF). This is neither a distinct nosological disorder nor a discrete diagnostic entity, but is based on subjective symptoms and disability.

None of the participating paediatricians from the different parts of the Netherlands had any reluctance to diagnose PUF. They recognised the lack of knowledge and were motivated to participate in this study.

The aim of the research conducted for this thesis was to answer the following research questions:

1. Which children and adolescents are seeking paediatric help for ongoing debilitating fatigue?
2. What is their prognosis?
3. Is a modelling video film intervention program, offered by the paediatrician, an appropriate addition to the usual management?

Fatigue might be the result of a health undermining way of living, characterized by too much burdening, too less rest, insufficient food, the use of substances, or family dynamics. We researched lifestyles, life events and family characteristics of the youngsters with prolonged, unexplained fatigue. Chapter 2 reports the findings.

Prolonged unexplained fatigue is accompanied mostly with other somatic complaints. Chapter 3 reports the findings and the relations between particular symptoms and the outcome of fatigue one year later.

Since several guidelines for regular physical exercises have been published to promote health, we studied the effects of the most common daily exercise in the Netherlands (i. e. cycling to school) and practising sports in and outside sports clubs on the persistence of fatigue. Chapter 4 reports the findings

Un-refreshed sleep is one of the key symptoms of adolescents with CFS, but also a complaint of many healthy youngsters. We studied and compared the quantity and subjective quality of sleep in the group PUF patients and in two fatigued and not fatigued groups of healthy controls. Chapter 5 reports the findings.

Outpatient care is the optimal treatment for the majority of youngsters with CFS with evidence for Cognitive Behavioural Therapy (CBT), Graded Exercise Therapy (GET) and avoidance of prolonged bed rest or complete inactivity. It is plausible that the same applies for those who do not (yet) fulfil the CDC criteria. However in daily practise there is often parental or patients reluctance against psychological interference besides organizational barriers to start CBT in an early stage of fatigue. Chapter 6 reports the results of a randomized controlled trial investigating the efficacy of a modeling video film intervention program in addition to treatment as usual.

A substantial percentage of the patients with prolonged unexplained fatigue will fulfil the CDC criteria in a later stage. In spite of the general thoughts that the prognosis for adolescent CFS is relatively good and better than for adults, the actual impairment at that age might be still severe. Literature on these items is not without debate. Chapter 7 reports the symptomatic and educational long-term outcome at 3.2 years after diagnosis of a group of adolescents with CFS in a third line CFS paediatric clinic.

In chapter 8 the results of these studies are linked together and put in a wider perspective with concluding remarks.

Dutch and Frisian summaries of the studies follow.

Chapter 2

Severe fatigued children and adolescents in general Paediatrics; Characteristics

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Abstract

Objectives To explore the role of life style factors, life events and family characteristics in children and adolescents with prolonged fatigue in general paediatrics.

Methods 93 patients in the age of 8 to18 years, who were referred to general paediatricians because of prolonged (not yet CFS) fatigue, completed questionnaires about fatigue, sleep, somatic premorbid symptoms, life style, life events, mental / physical load, and family characteristics.

Results Children and adolescents with ongoing fatigue reported also sleep problems and different somatic symptoms. They were educated at mean higher school levels and had serious school absence. Preceding the onset of fatigue they had relatively good school results, did not experience school work as overburdening, and had a life style with less physical (sports and additional jobs) and more sedentary (audiovisual, computer) activities. Although they reported to have a lot of good friends, they had little joint activities with them and went out very rarely. They were growing up in mean higher educated families with considerable more fatigued members and more frequently with separated parents. They had no health condition undermining eating habits nor substance use. They estimated the quality of relations with meaningful persons as good, but patients in one parent families generally qualified the relations with their parents as worse. Most patients had one ore more life events in the year preceding the fatigue complaints. In a follow up period of 12 months no medical or psychological explanations for the complaints have been found.

Conclusion Children and adolescents, referred to paediatricians because of fatigue might be familiar vulnerable by genetics and/or modelling attributions. Their premorbid life style was characterised by little physical activities and rarely going out, more sedentary and cultural/creative leisure activities and absence of unhealthy food habits or substance abuse. Compared to population studies, they did not overburden themselves and slept more hours.

Introduction

Complaints of fatigue are common subjective experiences and 11 to 33% of the first visits patients contact their general practitioner for complaints of persisting fatigue[1-3] and approximately 1 % of the adult Dutch population experiences Chronic Fatigue.[4] Also in youngsters fatigue is not rare. In a Dutch high-school based survey 13.5% of the youngsters reported fatigue.[5] In the USA and UK 'life time"(before 18 years) prevalence rates of CFS-like symptoms were reported of approximately 2%.[6-8] In a random digit dialing survey in the USA 0.34% of the adolescents reported to have CFS-like illness.[9] In a cross sectional study in the UK symptomatic fatigue in 5-15 years old was common, but chronic fatigue and CFS rare.[10] The large diversity of reported prevalences in the different studies might be caused by the different study designs and the different descriptions of chronic fatigue, but these studies and clinical practice make clear that persistent fatigue in youngsters is a serious problem. The last decades paediatricians seem to witness an increase in the incidence and prevalence of children and adolescents with severe fatigue complaints, often leading to very restricted physical and social life.[11] When fatigue persists for a longer period in adolescence the risk for a negative impact on education and psychosocial development arises.[12] Almost 50% of the patients referred by general practitioners to Dutch paediatricians because of prolonged unexplained fatigue were after one year still severe fatigued and 20.3 % missed still more than 50% school classes.[13] A thorough clinical evaluation did not clarify underlying or contributing conditions of somatic or psychiatric morbidity. Layman articles imply that chronic fatigue in adolescents is of epidemic proportions and related to today's life style with overburden, late bed times and unhealthy habits. The aim of this study was to explore possible common backgrounds to get a better understanding of patients with prolonged unexplained fatigue, who were referred to paediatricians.

Methods

Patients

Ninety-three patients in the age of 8-18 with the main symptom of severe fatigue and referred by their general practitioner to a general paediatrician for the first time, have been included through 2003-2006. Thirty paediatricians from 10 Dutch non-academic hospitals, both rural and urban, collaborated in this study by inviting the patients to participate. All patients

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underwent a thorough clinical evaluation by their paediatrician to identify possible underlying or contributing conditions of somatic or psychiatric morbidity. No underlying diseases were found that could explain their prolonged fatigue at baseline neither during the 12 months follow-up period. Written informed consent was obtained from all participating patients and or from their legal guardians.

The protocol of this study has been approved by the Medical Ethical Committee of the University Medical Centre Utrecht and the Regional Ethics Committees.

Measures

Questionnaires with instructions have been sent by post to the patients, who agreed to take part in the study.

Questions regarding complaints at the moment of referral

Fatigue was measured by The Checklist Individual Strength (CIS). This is a 20-item questionnaire and measures four aspects of fatigue during the last 2 weeks: fatigue severity (8 items, range 8-56), concentration problems (5 items, range 5-35), reduced motivation (4 items, range 4-28) and reduced activity (3 items, range 3-21). Each item was scored on a 7 point Likert scale. High scores indicate a high level of experienced fatigue, a high level of concentration problems, a low level of motivation and a low level of activity. The questionnaire has good reliability and discriminative validity.[14]

Somatic complaints were assessed with the validated Dutch translation of the Children s' Somatization Inventory (CSI). This is a self-report questionnaire rating the presence of 35 somatic symptoms in the last 2 weeks preceding the assessment, using 5 point Likert scales ranging from not at all (0) to a whole lot (4). A total score, representing both number and severity of symptoms was obtained by summing the ratings (range 0-140;35x4).[15]

School: absence percentage in the last month before referral was measured by dividing the missed classes by the scheduled classes.

Questions regarding (over)burden before the onset of fatigue

School: School level (lowest=1, vocational=2, high school=3, university=4), results (good, bad, in between) and difficulties with particular lessons (much, none, in between) and the own appraisal compared with classmates concerning load of home work (equal, more, less).

Time spent on regular cycling from home to school and physical exercises in sports.
Life events in last 12 months: move, new born in family, death or serious disease in family and beloved persons, unemployment in family, divorce of parents, break up friendship or courtship

Questions regarding rest at referral

Sleep was measured by a Sleep Questionnaire (appendix) regarding sleep latency, actual sleep time, subjective sleep need, and sleep problems such as unrefreshed, restless, wake ups during the night, light sleep and day time naps. This short questionnaire was developed for this study and offers insight into the quality of sleep perceived by the patients themselves.

Questions regarding leisure and relationships before onset of fatigue

Leisure activities: Time spent on activities such as physical activities, cultural activities, hobbies, going out (cinema, bars, dancing), jobs, watching television, playing computer games, wearing a walkman.
Friendships: number of close friends and frequency of joint activities.
Quality of relationships: The own appraisal compared with peers concerning the quality of relations with friends, parents, brothers / sisters and teachers (better, same, worse).
To be on your own: fine, moderate, boring.

Questions regarding family

Parents: age, level of education (elementary school=1, vocational training=3, high school=3 and university=4), current status of employment, country of birth and presence of fatigue complaints.
Family: one or two parent family, number of children, place in line of children, presence of fatigue complaints in brothers or sisters.

Questions regarding food and substance use

Food general evaluation: All meals, snacks and drinks used on two different weekdays in the period after referral. Answers have been qualified by research paediatrician in sufficient /moderate / deficient.
Substance use before the onset of fatigue: The number of glasses alcohol, cigarettes and (soft)drugs they used on weekdays and weekend days.

Data Analysis

Data analysis was performed using SPSS 14.0 (SPSS, Chicago IL, USA). Descriptive statistics were used to describe the distribution of relevant baseline patients characteristics with means and standard deviations. Differences between normally distributed datasets of the subjects and reference datasets were assessed by Student’s T-Test.

Results

Subject characteristics are presented in table 1. We included 93 patients aged 14.0 (SD 2.1) years. All patients were Caucasian and born in the Netherlands. The female percentage was 73.1%.

The fatigue complaints started 6.7 (SD4.8) months before paediatric referral. At referral the severity score was 46.7 (SD 8.8). That is evidently beyond the clinical cut off score of the CIS-20, id est 40 Likert points (scale 8-56) [14] The CIS-20 subscale scores for concentration, motivation and activity were significantly higher than the reported scores in healthy controls of the same age in the study of ter Wolbeek.[5] That means that the patients were experiencing more severe symptoms on these particular items at a lower level. They reported to need more sleep and naps, and slept actually with 8.9 hours (SD 1.7) longer than peer groups in literature (7.3-8.2 hours).[5,16] (to be published separately by the authors). Besides fatigue and sleep problems, the patients scored twice as much somatic symptoms compared with the healthy controls in the study of van de Putte.[17] Some of these somatic symptoms such as hot/cold spells, blurred vision, memory deficits, and constipation were risk factors for persisting fatigue one year later.[13]

Table 1: Subject characteristics. Means (SD) and percentages presented

Patients number =93	
Age (years)	14.0 (2.1)
Gender (% girls)	73.1
Born in the Netherlands (%)	100
Fatigue	
Duration of complaints (months)	6.7 (4.8)
Total score Checklist Individual Strength (CIS-20) (20 items, range 20-140)	96.2 (19.1)
Score subscale subjective fatigue (8 items, range 8-56)	46.7 (8.8)
Score subscale concentration (5 items, range 5-35)	21.7 (8.7)
Score subscale motivation (4 items, range 4-28)	16.4 (6.0)
Score subscale physical activity (3 items, range 3-21)	13.2 (5.0)
Somatic symptoms:	
Number somatic symptoms (0-35)	13.6 (6.9)
Children's Somatization Inventory (35 items; 0-140)	26.8 (14.3
Sleep	
Sleep needed (hours)	10.2 (1.7)
Actual sleep (hours)	8.9 (1.7)
Sleep problems (5 items 5-25)	13.9 (3.5)

Education is presented in table 2. Patients aged <12 years attended primary schools and no one received special education. Patients aged >= 12 years attended secondary schools with a mean education level above the level of the Dutch peer group[18] and reported to have experienced school as a not particularly heavy load. Comparing with classmates 16.1 % estimated their sense of effort to school work before the onset of fatigue as more and 20.4 % as less, and they qualified their results at school in more than 95 % better. In the last month before referral they missed more than half of the classes.

Table 2 Education; percentages presented

		Patients	Dutch references same age
Level of education patients >=12 year (%)	Level 1	0.0	10.0 (learning with special support)
	Level 2	52.4	50.0 (Vocational school)
	Level 3	47.6	40.0 (High school)
	Level 4	0.0	0.0 (University)
Load of home learning for school compared with classmates preceding onset fatigue (%)	Equal	63.4	
	More	16.1	
	Less	20.4	

		good	bad	in between
Results in school subjects preceding onset fatigue (%)	Alpha lessons	44.6	2.2	53.2
	Beta lessons	34.9	4.7	60.4
	Gamma lessons	37.5	2.3	60.2
	Practical lessons	22.7	3.9	23.4
Schoolabsence last month (%)	50.2			

One or more stressful events in the year before onset of fatigue were mentioned by 57 % of the patients: death of a grand parent or another member of family (34.0%), severe illness of a family member (26.0%) and break off a close friendship (28.2%).

Contacts in the last year with first line psychologists or school social workers were reported by 19.1 %, but only 3 patients (3.2%) were referred to the regional psychosocial/ psychiatric institutes (Jeugdzorg/ GGZ jeugd). That was below the 4.6% of the Dutch youngsters who are registered in these institutes.[19]

Lifestyle before onset of fatigue

Physical activities on regular basis were less than the average for peers (table 3). The patients were significantly less physical active in daily cycling to school (69.9 % versus Dutch mean 90%[18]) and in sports clubs (62.4% versus Dutch mean 71%[18]). Furthermore nobody was practising sports above the recreational level or had an additional job on regular basis. We found in an other study that membership of a sports club and daily cycling to school were protective factors against persistent fatigue one year later.[20]

Leisure activities of the patients above 12 years old (table 3). 52 % reported to have been active in the period before the onset of fatigue on regular basis in cultural and creative hobbies such as playing music, singing, painting or drawing. That is more than the 44 % for Dutch adolescents with cultural hobbies.[18] They spent 41.7 (SD34.3) minutes a day on these activities, and 12.1 % practised their hobby on a level and intensity that allowed them to participate in cultural performances or exhibitions. Besides these cultural occupations they reported to spend daily 71.2 (SD 58.5) minutes with computer games, and 204.3 (SD 131.7) minutes with watching television. That is more than the average of 120 minutes a day that adolescents are watching television.[18] Striking was the small frequency of social activities together with friends; 35.1 % had less than 1 activity with friends a week, and 68 % of the patients went never out in the weekends to cinema, disco, pub or youth centre. Most subjects reported to have no problems with being alone. Less than 9 % is bored to be alone.

Table 3: Characteristics physical and leisure activities of patients older than 12 years. Means (SD), percentages and reference values presented

	Subjects	Dutch reference values	*P-value*
Daily cycling home-school (%)	69.9	90	<0.001
Membership sports club (%)	62.4	71	<0.001
Regular jobs weekly > 12 hours(%)	0	15.0	<0.001
Cultural and creative hobbies (%)	52.0	44.0	<0.001
Watching television (minutes a day)	204.0 (131.0)	120	<0.001
Computer games (minutes a day)	71.2 (58.5)	-	
Activities with friends < once a week (%)	35.1	-	
Going out never (%)	68.0	-	
Going out never (%)	15.9	40	<0.001

Food and substance use. Generally the subjects of this study had good eating habits. According to the Dutch good food guidelines[21] the daily food intake, reported by patients themselves on 2 different days in the period after referral, was in 7.6 % not sufficient. Compared with the healthy high school students in the study of ter Wolbeek,[5] in patients of the same age in this study the substance use before onset of fatigue, was significantly less: 3.3% smoked cigarettes (versus 6.9%), no one drank alcohol on schooldays (versus13.2%), and 3.3% drank alcohol in the weekends (versus 43.9%).

Backgrounds

Family characteristics and comparison with known Dutch data are presented in Table 4. The families counted 2.3 children, corresponding to the mean Dutch family with children. The patients had no specific place of line of children; 16 % were only child; 14.3 % grow up with one parent, which is almost double as much as in Dutch autochthonous families.[22] Almost all parents were born in the Netherlands and were not particular young or old when they got the patient in question as their child. Fathers were 3 years older than mothers. More mothers participated in full time jobs than reference mothers; also more mothers did not work at all, but not significantly, and the average job participation was 15.0 hours a week corresponding with reference mothers. Fathers participated more in fulltime jobs and were less unemployed than reference fathers, and the average job participation was with 33.9 hours a week significantly more than reference fathers. Fathers worked more hours a week than mothers, while they were not significantly higher educated than mothers. [18,22,.23] Both parents were

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higher educated than the Dutch mean of their age group.[24] The same fatigue complaints were not rare in other family members; 19.8 % of the mothers, 8.8 % of the fathers and 12.1 % of the brothers and sisters complained of fatigue also. Compared to the 0.25-1.7 % prevalence in the general population these percentages are strikingly higher.[9,10,25] The female/male ratio of the prevalence of fatigue in parents was 2:1. That means that male gender was overrepresented compared with the usually reported female/male ratio of fatigue 3:1.[26,27]

Table 4: Family characteristics. Means (SD), percentages and reference values presented

		Subjects	Dutch reference values	*P-value*
Mother actual age		44.2 (3.8)		
Born in the Netherlands (%)		97		
Same fatigue complaints (%)		19.8		
Labour participation (%)	Full time	13.2	9.7	
	Part time	45.0	62.4	
	None	31.9	27.9	
Hours/ week work		15.0 (14.2)	15.0	

		Subjects	Dutch reference values	*P-value*
Father actual age		47.0 (5.2)		
Born in the Netherlands (%)		93		
Same fatigue complaints (%)		8.8		
Labour participation (%)	Full time	80.0	57.0	
	Part time	7.8	15.1	
	None	12.2	28.0	
Hours/ week work		33.9 (13.6)	23.3	<0.001

		parents	Dutch reference values	*P-value*
Both parents (born between 1955-1964) mean highest education level (%)	Level 1	1.6	7.8	
	Level 2	26.0	21.5	
	Level 3	40.3	43.5	
	Level 4	32.1	27.1	
Mean level of education both parents		3.04 (0.70)	2.88	0.033
Family				
One parent family (%)	14.3		7.4	<0.001
Number of children	2.3 (1.5)		2.3	
Only child (%)	16.1		10.0	<0.001
Same fatigue complaints in brothers/sisters (%)	12.1			

Relationships. 90 % reported to have two or more good friends and the same percentage estimated their relationships with parents, teachers and peers as equal or better than their peers should have with parents, peers and teachers, but 23 % of the patients, who were growing up in an one parent family, qualified their relation with parents as less good, while they qualified the relationships with peers and teachers as equal or better.

Discussion

In the present study the data are self-reported and assessed after the patients visited the paediatrician and no explanation for the fatigue has been found. That was on average 6.7 (4.8) months after the onset of the fatigue. They were asked for an estimation of their activities before the onset of fatigue. This might have introduced differential recall bias. In addition, questions, regarding one’s own estimating and comparing with peers, might be replied too rose-coloured. Furthermore in 51 % one of the parents, almost always the mother, was helpful with filling-in the questionnaires. Thus the perception of the mother might have influenced the results also. Retrospective research by questionnaires about life style before the onset of fatigue, some months later, limits the study. Nevertheless, this study aimed to get an impression of patients with prolonged unexplained fatigue, who were referred to paediatricians.

The patients had besides the severe fatigue complaints a substantial number of serious somatic complaints, sleep problems and serious school absenteeism. They were considered by parents and /or by themselves as ill and were seeking medical help first by their general practitioner and after that by a paediatrician.

They followed education on mean higher school levels and no one on the lowest level. Most patients had no difficulties with lessons or home work and had good and sufficient marks before the onset of illness. It seems, that school was not overburdening, but to conclude that is not clear, because patients might have had misconceptions about their sense of effort for school tasks.

The physical activity was objectively less than the average for this age and in spite of the possibility that that is still too much for some youngsters, it seems very unlikely that physical activities were overburdening.

There were hardly patients with health condition undermining and illness provoking eating habits, smoking, use of alcohol or (soft) drugs. They seemed to be ‘model youngsters’ in that way.

Almost half of the patients reported one or more stressful life events in the past year. Most events consisted of broken close friendships relations, serious illness in the family or dead of a grandparent. Life events and elevated stress are known to be associated with provoking chronic fatigue.[28,29] Children with divorced parents were overrepresented, and a quarter of them qualified the relation with their parents as not good and a half mentioned to receive psychological help. Because the quality of relations with meaningful persons is predictive for psychological and social wellbeing,[30] it is likely that this is a weight giving factor also.

Rest and relaxation by recreational leisure activities counterbalance physical and mental loads. The patients in this study had less physical activities in sports clubs or by going out, but more sedentary activities by watching television, computer games and listening to music. On the other hand also a majority had cultural and creative activities at home on regular basis. Remarkable is the great discrepancy between the substantial number of good friends and the very few activities together with them. It looks like good friendships are more a rose-coloured imagination than reality. In any case they did not provide social activities. These findings together could indicate that the patients were more addressed to themselves than to peers.

The aggregation of same fatigue complaints in the family might have been influenced by genetic transfer and modelling attributions to a shared symptom complex by structure, functioning and dynamics of the family.[31,32] In this respect, the relatively high percentage of fatigued fathers is remarkable. Parents were higher educated, and especially the higher job participation of the fathers might indicate that these families have a higher ambition level and a higher sense of responsibility that influence family dynamics.

The pathophysiology of ongoing fatigue in youngsters is still hardly understood. Many mechanisms have been postulated and are suggestive for a multi factorial cause of the illness. One of the presuppositions is today’s overloaded life style of young people. However, with the present findings in fatigued children and adolescents, they are characterised rather as ‘model youngsters’, good learning without unhealthy food or substance habits and without late bedtimes. They did not overburden themselves with physical or mental activities. In contrary, they spent more time on sedentary audiovisual occupations and on cultural and creative hobbies. They participated less in social activities in spite of experienced good relationships and friendships. We found indications that family dynamics and/or genetic factors increase the vulnerability, that stressors like life events may be provoking factors, and that the social environment is not helpful in resistance against slide down into chronic fatigue. It seems that a substantial number of patients, notwithstanding the incidence of intercurrent illness, will loose their faith in the possibilities of physicians to help them, and address themselves to alternative medicine.

The layman opinion that epidemic proportions of chronic fatigue in adolescents are related to today’s overloaded life style, late bed times and unhealthy habits is not supported by this study.

Severe fatigue in childhood and adolescents is a serious problem that needs a treatment focused not only on the fatigue complaints, but especially also on the development of social skills.

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Chapter 3

Risk factors for Persistent Fatigue with or without significant School Absence in children and adolescents

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Abstract

Objective To assess children and adolescents with severe fatigue who are referred to pediatricians and to examine whether factors can be identified at their first visit that predict worse outcomes at 1 year.

Methods 91 patients, aged 8 to18 years, referred to a pediatrician in a general hospital with complaints of severe fatigue completed questionnaires about sleep, somatic symptoms, physical activity and fatigue. They were reassessed 12 months later. Measurements at baseline and outcome parameters 12 months later were analyzed using univariable logistic regression with persistent severe fatigue (yes/no) and persistent school absence (yes/no) as dependent and baseline scores as independent variables.

Results After 12 months only 50.6% of children and adolescents showed improvement; 29.1 % had persistent fatigue without school absence and 20.3 % had persistent fatigue with significant school absence. Factors associated with the poorest outcome were: sleep problems (OR 1.4; CI 1.1;1.8), initial fatigue score (OR 1.1; CI 1.0;1.2), somatic complaints such as hot/cold spells (OR 1.9; CI 1.2;3.0), blurred vision (OR 2.1; CI 1.1;4.0), pain in arms and legs (2.0; CI 1.0;3.2), back-pain (OR 1.8; CI 1.0;3.2), constipation (OR 1.7;CI 1.0;2.7) and memory deficits (OR 1.8; CI 1.0;3.2). Resolved fatigue was associated with male gender (OR male 5.0; CI 1.6;15.5) and a physically active lifestyle (OR 1.3; CI 1.1;1.5).

Conclusions Assessment of predictive factors at the first visit enables the pediatrician to identify those children and adolescents with severe fatigue who are at risk of a poor outcome. Female gender, poor sleep quality, physically inactive lifestyle and specific somatic complaints were important predictive factors.

Introduction

Fatigue is a universally experienced but not well understood symptom. In a Dutch survey of an adolescent school-based population, 20.5% of the girls and 6.5% of the boys reported severe fatigue, of whom 80% and 61.5% respectively, reported fatigue lasting one month or more.[1] In most cases the fatigue will disappear spontaneously over time. A small percentage of fatigued adolescents will seek medical advice. For these patients it is of great importance to know risk factors for the persistence of fatigue. Persistent fatigue has a negative impact on education and career plans, particularly through failure to attend school.[2-4] Most studies on fatigue focus on the Chronic Fatigue Syndrome (CFS) as defined by the Chronic Fatigue Syndrome Study Group.[5] Little is known about children and adolescents who do not meet CFS criteria, but nevertheless have complaints of ongoing debilitating fatigue and are seeking medical help. The purpose of our study was to determine those factors that predict the outcome for children and adolescents who present to the pediatrician with fatigue as their most dominant symptom.

Lack of refreshing sleep is one of the key symptoms of CFS.[5] Moreover, fatigued adolescents experience a variety of physical complaints such as headaches, muscle and joint pains and abdominal pain.[6-9] Both poor sleep quality and these concomitant somatic symptoms might be associated with poorer outcomes for children and adolescents with fatigue. The level of exercise prior to onset of fatigue may be another important prognostic factor. Little[10] and much [11-13] physical activity in sport both are known risk factors for the development of Chronic Fatigue.

We assessed the associations between gender, severity of fatigue, sleep quality, somatic symptoms and physically active lifestyle at baseline and the persistence of fatigue with or without significant school absence in the subsequent year.

Methods

Participants

Ninety-one patients aged 8 to 18 referred to one of 30 pediatricians from 10 Dutch non-academic hospitals between 2003 and 2006 with the main symptom of disabling fatigue were included. All patients underwent a thorough clinical evaluation by their pediatrician to identify possible underlying or contributing conditions of somatic or psychiatric morbidity. In the study period (12 months) none of the patients received a final medical explanation for the fatigue complaints. At the first appointment and after 12 months the patients filled out questionnaires at home. The general treatment by the pediatrician consisted of reassurance and encouragement to attend school as much as possible. Half of the patients received, as part of a randomized controlled trial, a video film about chronic fatigue and how to cope with it.

Measures

Outcome variables: Fatigue was measured at baseline and at 12 months, with the subjective fatigue subscale of the validated Dutch version of the self-report questionnaire Checklist Individual Strength (CIS-20), which consists of 8 items about fatigue experienced in the 2 weeks preceding the assessment, using 7-point Likert scales (range 8-56 points). The questionnaire has good reliability and discriminative validity.[14] Persistent fatigue was defined as a subjective fatigue subscale score of >= 40 on the CIS-20 at 12 months, and persistent fatigue with significant school absence was defined as persistent fatigue plus a school absence of > 50%. School absence was measured by missed school classes divided by the total number of scheduled classes in the past 4 school weeks.

Predictive variables: Somatic complaints were assessed at baseline with the validated Dutch version of the Childrens' Somatization Inventory (CSI),[15] a self report questionnaire, rating the presence of 35 somatic symptoms in the 2 weeks preceding the assessment, using 5-point Likert scales. A total score, representing both number and severity of symptoms was obtained by summing the ratings (range 0-140).

Sleep problems were measured at baseline and at 12 months by a Sleep Questionnaire (appendix). This short questionnaire was developed for this study and offers insight into the quality of sleep as perceived by the children and adolescents themselves. Each item was scored on a 5-point Likert scale (1-5). The total score was obtained by summing the ratings (range 5-25). The higher the score, the more sleep problems exist.

Physical activity as part of the lifestyle before onset of the fatigue complaints was measured by a questionnaire, with 6 items asking about regular exercise in the year preceding the fatigue adding up to a total score between 0 and 15 (appendix). The membership of sports clubs is a separate item as, in the Netherlands, sports clubs are not related to schools and membership points at a more active lifestyle within a social context. Separate validation studies for the sleep quality and physical activity questionnaires were not performed.

The medical ethics committee of the University Medical Centre Utrecht approved the protocol of this study. Assent was obtained from all patients and/or their legal guardians.

Data Analysis

For the distribution of baseline patient characteristics and baseline data of fatigue, sleep and somatic symptoms, descriptive statistics were used (means and standard deviations).
To identify predictive factors at baseline for the persistence of fatigue with or without school absence 12 months later, the data were analysed with univariable logistic regression using the CIS-20 subjective fatigue subscale >=40 (yes/no), CIS-20 subjective fatigue subscale >=40 plus significant school absence (>50%) (yes/no), and resolved fatigue (yes/no) at 12 months follow-up respectively as dependent variables. 'Regular exercise', 'Sleep Quality score', 'Childrens' Somatization Inventory score', and 'specific somatic symptoms' were analysed as independent variables. Multivariable logistic regression with the same outcome variables was used to examine the independence of factors that were univariably associated with outcome measures. Results are expressed as odds ratios and 95% confidence intervals (CI) adjusted for age and gender, indicating the odds of having the dependent variables after 12 months, in the presence of the factor or symptom compared to the absence of that factor or symptom at the first visit, irrespective of age and gender. Statistical significance was considered to be reached when the 95% confidence intervals did not include 1, corresponding to a p-value <0.05.
All analyses were performed using SPSS 14.0 (SPSS, Chicago IL, USA).

Results

Ninety-one patients (72.5% girls) were included with a mean age of 14.0 (SD 2.1) years. All patients were Caucasian. Fatigue complaints started 6.7 months (SD 4.8) before the first visit to the pediatrician (median 5.0 months). At follow-up 12 months later, 79 patients (72.1% girls, age 15.0 (SD 2.0) year) participated in the study (86.8%). Table 1 shows the baseline characteristics of the total group of patients and of the three different outcome subgroups. After 12 months perceived severity of fatigue of the total group was decreased from a score of 46.7 (SD 8.8) to 36.1 (SD 14.1), school absence from 50.1 to 19.4 % (SD 30.4), and sleep quality from a score of 13.8 (3.4) to 13.1 (SD 3.5).
Table 2 shows predictors for the outcome at 12 months expressed as odds ratios. At 12 month follow-up, 23 patients (29.1%) had a fatigue severity score of ≥ 40 Likert points, without significant school absence. They were classified as persistent fatigue. Sixteen patients (20.3%) were classified as persistent fatigue (≥ 40 Likert points) with significant school absence. In 40 patients (50.6%) the fatigue was resolved.

The odds of developing persistent fatigue with significant school absence were 40 % (OR 1.4; CI 1.1;1.8) higher for one Likert point increase on the sleep quality questionnaire and 10 % (OR 1.1; CI 1.0;1.2) higher for one Likert point on the subjective fatigue subscale. A physically active lifestyle before the onset of fatigue reduced the odds of persistent fatigue with significant school absence by 30% (OR 0.7; CI 0.5;0.9), being a member of a sports club reduced the odds by 90% (OR 0.1; CI 0.0;0.5); and regular cycling from home to school (mean 36.6 (SD 38.0) minutes a day) reduced the odds by 60% (OR 0.4; CI 0.2;0.8). The CIS-20 and the total score of the CSI did not predict persistent fatigue with significant school absence. Nevertheless, some somatic symptoms such as ‘blurred vision’ (OR 2.1; CI 1.1;4.0), ‘hot / cold spells’ (OR 1.9; CI 1.2;3.0), ‘memory deficits’ (OR 1.8; CI 1.0;3.2), ‘constipation’ (OR 1.7; CI 1.0;2.7), ‘pain in arms and legs’ (OR 2.0; CI 1.0;3.2) and ‘back-pain’ (OR 1.8; CI 1.0;3.2) were significantly associated with persistent fatigue with significant school absence.

The odds of developing persistent fatigue without school absence were also 10 % (OR 1.1; CI 1.0;1.2) higher for one Likert point on the subjective fatigue subscale. Despite being a predictor for persistent fatigue with significant school absence, sleep problems and previous physically active lifestyle did not predict persistent fatigue without significant school absence. Neither was the CSI total score predictive, but some somatic symptoms from the CSI: ‘Low energy’ (OR 2.6; CI 1.2;5.4), ‘walking difficulties’ (OR 2.1; CI 1.1;3.7), ‘knee / elbow pain’ (OR 1.8; CI 1.1;2.8) and ‘fainting’ (OR 4.2; 1.0;7.1) were significantly predictive for persistent fatigue without significant school absence.

Recuperation was significantly associated with being male (OR male 5.0; CI 1.6;15.5), previous physically active lifestyle (OR 1.3; CI 1.1;1.5), membership in sports clubs (OR 2.1;CI 1.0;4.3), and cycling home-school (OR 1.8; CI1.0;3.3). Recuperation was adversely associated with severity of fatigue at baseline (OR 0.9; CI 0.8;1.0) and initial presence of sleep problems (OR 0.8; CI 0.7;1.0).

Discussion

Fatigue in adolescents is quite common and in most cases the fatigue will disappear spontaneously over time.[1] Only a small percentage of fatigued adolescents will seek medical advice.[16] In the Netherlands, the fatigued adolescents will first consult their general practitioner for advice and examination. In case of ongoing fatigue, the general practitioner will then refer the patient to a general pediatrician, who will investigate further, excluding underlying somatic illnesses and psychological problems, and reassure the patient and parents. In most cases the general pediatrician will advise the patient to avoid complete inactivity, engage in a moderate level of exercise, and attend school as much as possible. However, the prognosis is not always good. If the predictive factors for a poor prognosis were known at the first visit, patients with increased risk of poorer outcome could be referred at an early stage for evaluation and management.

In this group of children and adolescents referred to general pediatricians for fatigue, we found that 49.4% (60% of the included female patients) had ongoing serious fatigue after 12 months. Female gender was a very strong predictor of a more severe outcome. The percentage of persistent fatigue patients was much higher than in a school based group of fatigued children,[13] where 25.7% of the children were persistently fatigued after one year. Not all of the persistently fatigued patients in our study developed significant school absence, with only 16 patients (20.3) missing more than 50% of their classes.

The patients in our population scored high on the Childrens' Somatization Inventory. This finding corresponds with the substantial overlap of chronic fatigue and somatization syndrome in a general population survey.[17] However, the total score on this Inventory did not represent a risk factor for poor outcome after 12 months, unlike some particular symptoms. 'Hot/cold spells', 'blurred vision' and 'memory deficits' were strong predictive factors for a more negative outcome. These features are part of a complex of symptoms connected to autonomic defects, such as orthostatic intolerance and thermoregulatory dysfunction. Orthostatic intolerance has been described in subgroups of adolescents with CFS.[18-21] The patients in our study were not examined by skin cooling tests and head-up tilt tests. The aim of the study was to find symptoms in the history of the patient which could be assessed at the first pediatric visit, instead of extensive testing of possible symptoms of autonomic dysfunction.

As known from the literature, sleep problems are associated with CFS [22,23] and lack of refreshing sleep is one of the defining features of the illness.[6] The patients in our study were characterized by more sleep problems at the initial evaluation. The more sleep problems at baseline, the higher the probability of developing unfavorable outcomes.

The patients in our population reported little physical activity on a regular basis before their illness. In the Netherlands, 71% of adolescents are members of one or more sports clubs.[24] Thirty-two percent of the patients who developed persistent fatigue with school absence were member of a sports club before their illness, compared with 75 % of the patients who had a more favorable outcome. These findings have striking similarities with the recently published paper of Viner et al, in which they describe both being highly sedentary or highly active as risk factors for persistent fatigue in adolescents.[25] In our population only 2 patients were highly active in the period preceding the fatigue. The finding that severely fatigued children with a moderately active lifestyle, especially in sports clubs, have higher probability of a relatively good outcome corresponds also with a cohort study that showed a strong negative association between playing sports on a regular basis in youth and CFS later in adult life.[11]

Our findings show that prior physically inactive lifestyle, sleep problems at baseline and some specific somatic symptoms predict the development of persistent fatigue with significant school absence after 12 months. These factors could easily be recognized at the first visit and enable earlier evaluation and management. However, intervention studies aimed at preventing persistent fatigue with considerable school absence have not been performed yet. Cognitive behavior therapy might be effective, as it is has been shown to be effective for adolescents with CFS.[26]

In conclusion, our study shows that fatigued children and adolescents seeking medical care from a general pediatrician are at risk of developing persistent fatigue with significant school absence one year later. This has a serious implication for education, career and psychosocial skills. We identified specific factors that predict this serious outcome. The group of fatigued children and adolescents with these factors will need interventions to prevent this outcome.

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Appendix

Questionnaires

(interpreted and completed by patients themselves)

Sleep Problems

How often *never-seldom-sometimes-often-always* (1-5)

Do you wake up un-refreshed?

Do you have a restless sleep?

Do you wake during the night?

Do you have a light sleep?

Do you take daytime naps?

Total score Sleep Problems (5-25)

Physical Activity

Sports Club membership	(0-2)	*none-one- more than one*
Frequency of training	(0-2)	*never- one time- more than one time a week*
Participation in contests	(0-2)	*never- one time- more than one time a month*
Level of sport practice	(0-2)	*not applicable-recreational-(sub)top*
Daily cycling (season)	(0-2)	*never-only in summer-always*
(time)	(0-3)	*none-<15 min.-15 to 30 min.-> 30 min.*
Daily exercise beside sports club	(0-2)	*never- one time- more than one time a week*
Total Regular Exercise score	(0-15)	

Table 1 Characteristics of fatigued patients at baseline (total group and classified in the outcome scores: resolved, persistent fatigue with and persistent fatigue without school absenteeism) and at 12 months follow-up. Means (SD) and percentages presented

	At base line				**at 12 months**
	Total group N=91	Resolved fatigue patients N=40	Persistent fatigue patients without school absenteeism N=23	Persistent fatigue patients with school absenteeism N=16	Total group N=79
Age	14.0 (2.1)	13.8 (2.2)	14.4 (1.8)	14.1 (1.7)	15.0 (2.0)
Gender (%girls)	72.5	57.5	91.3	81.2	72.1
Total score CIS-20 (20 items ;20-140)	96.2 (19.1)	88.4 (21.1)	102.9 (13.9)	100.2 (15.7)	80.0 (28.6)
Score subjective fatigue subscale (8 items; 8-56)	46.7 (8.8)	42.3 (9.3)	49.7 (6.0)	49.4 (5.7)	36.1 (14.1)
Fatigue complaints duration (months)	6.7 (4.8)	6.6 (5.4)	6.6 (5.4)	10.3 (6.7)	19.1 (5.1)
Total score Childrens' Somatization Inventory (35 items; 0-140)	26.8 (14.3)	21.7 (12.2)	30.4 (13.6)	30.6 (13.5)	
School absence (%)	50.1 (45.5)	42.5 (45.7)	47.8 (45.1)	67.1 (44.4)	19.4 (30.4)
Total score Sleep Problems (5 items; 5-25)	13.8 (3.4)	12.6 (2.8)	13.9 (3.1)	15.4 (3.5)	13.1 (3.5)
Un-refreshing sleep (1-5)	3.9 (1.0)	3.6 (1.1)	4.0 (0.9)	4.2 (0.8)	3.6 (1.0)
Restless sleep (1-5)	2.8 (1.0)	2.6 (1.0)	2.8 (1.0)	3.1 (1.0)	2.7 (1.1)
Wake up during night (1-5)	2.6 (1.0)	2.3 (0.8)	2.7 (1.1)	2.8 (1.0)	2.5 (1.1)
Light sleep (1-5)	2.4 (1.1)	2.2 (1.0)	2.3 (1.1)	2.8 (1.2)	2.4 (1.1)
Taking daytime naps (1-5)	2.2 (0.8)	2.1 (1.1)	2.3 (1.1)	2.1 (1.2)	2.0 (1.0)
Sleep latency (minutes)	50.2 (48.3)	42.4 (38.7)	51.3 (43.5)	40.6 (17.2)	
Physical activity scale in year before illness (0-15)	6.4 (3.2)	7.5 (3.0)	6.3 (2.8)	3.9 (3.2)	

Table 2 Associations between the outcome at 12 months and sleep problems, previous physical activity, fatigue severity and somatic symptoms at baseline

	Resolved fatigue N=40		Persistent fatigue N= 23		Persistent fatigue with school absence N=16	
	Odds Ratio (CI) adjusted	p-value	Odds Ratio (CI) adjusted	p-value	Odds Ratio (CI) adjusted	p-value
Female gender	0.2 (0.1;0.6)	0.005	5.1 (1.1;23.8)	0.036	1.7 (0.4;6.7)	0.424
Sleep problems	0.8 (0.7;1.0)	0.050	1.1 (0.9;1.4)	0.354	1.4 (1.1;1.8)	0.014
Physical activity scale	1.3 (1.1;1.5)	0.003	0.8 (0.7;1.0)	0.096	0.7 (0.5;0.9)	0.002
Membership sports club (Y/N)	2.1 (1.0;4.3)	0.036	0.8 (0.4;1.7)	0.580	0.1 (0.0;0.5)	0.003
Cycling home-school (Y/N)	1.8 (1.0;3.3)	0.045	0.6 (0.3;1.2)	0.137	0.4 (0.2;0.8)	0.016
CIS-20 (SD)	1.0 (0.9;1.0)	0.008	1.0 (1.0;1.1)	0.015	1.0 (1.0;1.1)	0.082
Subjective fatigue subscale (SD)	0.9 (0.8;1.0)	0.002	1.1 (1.0;1.2)	0.009	1.1 (1.0;1.2)	0.025
Childrens' Somatization Inventory (SD)	1.0 (1.0;1.0)	0.019	1.0 (1.0;1.1)	0.056	1.0 (1.0;1.1)	0.060
Somatic symptoms:						
Low energy (Y/N)	0.5 (0.3;0.8)	0.006	2.6 (1.2;5.4)	0.011	1.8 (1.0-3.4)	0.078
Hot / Cold spells (Y/N)	0.6 (0.4;0.9)	0.008	1.5 (1.0;2.2)	0.070	1.9 (1.2;3.0)	0.007
Blurred vision (Y/N)	0.6 (0.4;1.1)	0.110	1.2 (0.6;2.4)	0.587	2.1 (1.1;4.0)	0.027
Defective memory (Y/N)	0.7 (0.4;1.2)	0.161	1.1 (0.5;2.0)	0.872	1.8 (1.0;3.2)	0.039
Fainting (Y/N)	0.4 (0.0;1.1)	0.114	4.2 (1.0;7.1)	0.049	1.6 (0.4;6.0)	0.463
Constipation (Y/N)	0.6 (0.4;1.0)	0.039	1.9 (1.0;3.6)	0.051	1.7 (1.0;2.7)	0.050
Walking difficulties (Y/N)	0.5 (0.1;0.9)	0.027	2.1 (1.1;3.7)	0.016	1.8(1.0;3.4)	0.094
Pain in arms and legs (Y/N)	0.6 (0.3;0.9)	0.027	1.6 (1.0;2.7)	0.105	2.0 (1.0;3.2)	0.029
Back pain (Y/N)	0.8 (0.6;1.3)	0.440	0.9(0.5;1.5)	0.615	1.8 (1.0;3.2)	0.041
Pain in knee and elbow (Y/N)	0.7 (0.5;1.1)	0.101	1.8 (1.1;2.8)	0.013	0.9 (0.5;1.6)	0.663
Nausea (Y/N)	0.6 (0.3;1.0)	0.040	1.3 (0.8;2.0)	0.286	1.3 (0.7;2.3)	0.353
Tingling (Y/N)	0.6 (0.4;1.0)	0.047	1.5 (0.9;2.6)	0.137	1.6 (0.9;2.9)	0.084

Adjusted: adjusted for age and sex. CI: confidence interval

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Chapter 4

Exercise in social context contributes to a favorable outcome in fatigued children and adolescents

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Introduction

Children might develop a healthy lifestyle by physical exercise in sports and – typically Dutch - in regular cycling to school. The effects of exercise, however, on fatigue are not without debate. In adults, both little[1] and much[2] physical exercise have proven to be a risk factor for the development of Chronic Fatigue Syndrome. The aim of this study in fatigued youngsters was to investigate the influence of club-based and self-regulated sports activities and regular cycling in the period preceding fatigue on the persistence of fatigue.

Methods:

Ninety-one patients (8 to18 years) with ongoing fatigue referred to a general paediatrician have been included and followed during one year.
At baseline, fatigue and activity were measured with the subjective subscale scores of the validated Dutch version of the Checklist Individual Strength (CIS-20)[3], school absenteeism in the last month by dividing missed classes by scheduled classes, and physical exercises in the period preceding fatigue retrospectively by a questionnaire consisting of the following items: Membership of sports clubs (y/n), self-regulated activities not in sports clubs (y/n), regular cycling to school (y/n), and the time spent on these activities.
At 12 months, 'persistent fatigued' was defined as fatigue subscale score >=40 and 'resolved fatigued' <40.

Results

At 12 months, complete data for 79 patients (72.1% girls) were returned. At inclusion patients mean age was 14.0 (SD2.0) years, CIS-20 fatigue score: 46.2 (SD8.4), activity score:12.8 (SD5.1), school absenteeism 49.1% (SD45.7), membership sports club 63.3%, self-regulated sports activities 40.3%, and cycling to school daily (43.6 (SD36.8) minutes) 67.1 %. Initial characteristics of missed patients were not significantly different. Except from cycling, exercises were not significantly associated with fatigue severity at assessment. At 12 months 49.4% had 'persistent fatigue' and 50.6% had 'resolved fatigue' (subjective fatigue severity respectively 48.4 (SD5.4) and 24.1 (SD8.6)). Children with 'resolved fatigue' were more likely to have less fatigue at assessment (OR 1.1, CI 1.0;1.2, p0.002). Further analysis included the initial fatigue score, age and gender as possible confounding factors. Being a sports club member reduced the odds to develop 'persistent fatigue' with 70% (OR 0.3; CI

0.1;1.0) just as regular cycling to school (OR 0.3; CI 0.1;1.0). Practicing self-regulated sports activities was not significantly associated with the outcome of fatigue. The time spent on each of the 3 different physical activities was neither associated with fatigue severity at baseline nor at follow-up.

Comment

Membership of sports clubs and regular cycling to school preceding fatigue strongly improved the prognosis of fatigue, but self-regulated exercises did not. These differential effects on the course of fatigue might be explained by the fundamental differences between club-based and self-regulated sports activities. Exercises in sports clubs are regular activities in a socially embedded structure. Cycling to school is besides the daily exercise likewise a social activity, because most students are cycling with peers. Participation in clubs and groups strengthens self-esteem in children and adolescents[4] and supports regularity of activities. Conclusions from this study are limited by the fact that data on activity are self-reported and assessed at the moment that the patients were referred because of fatigue. This might have introduced differential recall bias. That was the reason to calculate adjusted odds. We can not adjust for a possible difference in perceived and actual time spent on activity. Membership of sports clubs, however, is a binary answer option with little opportunity for bias.

Our results suggest that it is possible that the social context of exercises with peers is more important for a favorable development of fatigue than merely exercises.. This could explain the discrepancies in the effect of exercise on fatigue in CFS studies.[1,2]

Table: Premorbid characteristics and differences at baseline between patients with the outcome resolved or persistent fatigue, and the odds ratios for the outcome persistent fatigue at 12 months follow up in children and adolescents seeking paediatric help for fatigue

	At baseline							
	Total Group N=79	Resolved fatigue N=40	Persistent fatigue N=39	Difference p-value	Odds Ratio (95% CI) for persistent fatigue	p-value	Odds Ratio (95%CI) for persistent fatigue, adjusted	p-value
Age (years)	14.0 (2.0)	13.8 (2.2)	14.3 (1.7)	0.238	1.1 (0,9;1.4)	0.237	1.0 (0.8;1.3)	0.926
Gender (%girls)	72.1	57.5	87.2	0.003	5.0 (1.6;15.5)	0.005	4.9 (1.4;17.0)	0.013
Initial score subjective fatigue CIS-20 subscale (8 items; 8-56)	46.2 (8.4)	42.8 (9.3)	49.6 (5.8)	<0.001	1.1 (1.0 ;1.2)	0.001	1.1 (1.0 ;1.2)	0.002
Initial score activity CIS-20 subscale (3 items; 3-21)	12.8 (5.1)	11.8 (5.2)	13.8 (4.9)	0.079	1.1 (1.0;1.2)	0.081	1.0 (0.9;1.1)	0.995
School absenteeism (% missed classes)	49.1 (45.7)	42.6 (45.7)	55.9 (45.2)	0.198	1.0 (1.0;1.0)	0.195	1.0 (1.0;1.0)	0.851
Membership sports club (% yes)	63.3	75.0	51.3	0.029	0.4 (0.1;0.9)	0.031	0.3 (0.1;1.0)	0.045
Time spent on club-based sports activities (minutes/week) In case of membership = yes	108.9 (74.0)	115.5 (59.4)	99.0 (92.5)	0.445	1.0 (1.0;1.0)	0.747	1.0 (1.0;1.0)	583
Self-regulated sport activities (% yes)	40.3	43.6	36.8	0.552	0.8 (0.3;1.9)	0.546	0.6 (0.2;1.9)	0.427
Time spent on self-regulated sport activities * (minutes/week) In case of self regulating sport = yes	173.9 (184.0)	152.1 (182.0)	200.4 (189.7)	0.623	1.0 (1.0;1.0)	0.629	1.0 (1.0;1.0)	0.782
Regular cycling to school (% yes)	67.1	73.1	37.7	0.002	0.2 (0.1;0.6)	0.004	0.3 (0.1;1.0)	0.042
Time spent on cycling to school (minutes/day) In case of regular cycling = yes	43.6 (36.8)	41.4 (39.0)	47.2 (36.8)	0.273	1.0 (1.0;1.0)	0.933	1.0 (1.0;1.0)	0.479

Persistent fatigue: Score subjective fatigue subscale (8 items; 8-56) >=40 Likert points.
Resolved fatigue: Score subjective fatigue subscale (8 items; 8-56<40 Likert points.
Adjusted : adjusted for age, gender and initial score subjective fatigue subscale. CI=95% confidence interval.
* running, swimming, fitness, (roller)skating etc.

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Chapter 5

Fatigue and sleep in adolescents: a comparative study in fatigued and non-fatigued adolescents

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Abstract

Objective The purpose of the study was to assess the relation between fatigue and sleep parameters in adolescents.

Methods In this cross-sectional study sleep parameters of 3 groups of adolescents were compared: 82 patients with Prolonged Unexplained Fatigue, 33 fatigued controls and 239 non-fatigued controls. Investigated sleep parameters were: estimated need for sleep, actual sleep time, sleep latency, and sleep problems. Questionnaires regarding fatigue and sleep parameters were applied to the adolescents.

Results 12.1% of healthy controls complained of serious fatigue. All adolescents, patients and controls, stated to have sleep shortage. Fatigued controls were – in comparison with not fatigued controls - older and more often girls. They estimated the same need for sleep, but slept actually shorter with more irregularity between week and weekend nights and with more sleep problems. Patients were younger than fatigued controls and more often girls as were the fatigued controls. Patients reported the most need for sleep, the most actual sleep time and the most sleep problems of the 3 groups.

Conclusion Fatigue, that develops into a referral to paediatrics arises earlier in adolescence than 'normal' fatigue in healthy adolescents. Gradual increase of sleep problems accompanies increase of debilitating fatigue. Changing sleep habits by increasing shortage and irregularity are associated not only with increase of fatigue, but also with increase of sleep problems. The promotion of sleep hygiene early in adolescence may be effective for the prevention of sleep problems and fatigue and a meaningful part of the management of prolonged unexplained fatigue.

Introduction

In adolescence fatigue and sleep complaints become more common.[1-3] In high school-based populations, 13.5% reported fatigue lasting 1 month or more,[4] and 35.7 % reported persistent sleep problems.[5] Sleep is the physiological need for recovering from fatigue. When the quantity is insufficient and/or the quality is unsatisfactory the sleep will not be restorative. Fatigue, caused by physical and mental exercises will generally be released by enough sleep, but sleep has not such a recuperating effect in patients with chronic fatigue. The fatigue is not resolved by the precedent sleep and unrefreshed sleep is one of the key symptoms of Chronic Fatigue Syndrome.[6] Fatigue and sleep complaints are subjective and self-reported phenomena. Despite the clinical evidence of decreased sleep quality in CFS patients there is a discrepancy between subjective sleep complaints and objective polysomnographic results. Objective assessments of sleep quality are not without debate.[7-10] The subjective description of the quality of the unrefreshing sleep by patients involves the estimated need for sleep versus the actual hours, sleep latency, restlessness during sleep, waking during the night, depth of sleep and the tendency to daytime naps. The most common reported complaints about sleep in chronic fatigued adolescents are frequently waking during the night,[11,12] excessive sleep need,[12,13] difficulty falling asleep[12,14,15] and daytime napping.[14,16]

In spite of the substantial percentages of adolescents in polls who report fatigue and sleep problems, only a small percentage has attributions and complaints that urge them to seek help in paediatrics. This leads to the question whether subjective sleep quality and quantity differs between 3 groups of adolescents: healthy non-fatigued adolescents, healthy fatigued adolescents and prolonged unexplained fatigued (PUF) adolescents seeking medical help. In this study we compared the subjective sleep parameters in these 3 groups.

Subjects

A group patients (N=82) in the age of 12 to18 year, referred by their general practitioner to a paediatrician because of prolonged unexplained fatigue (PUF) and 272 healthy controls in the same age group, subdivided in a group without complaints of fatigue (N=239) and a group with complaints of fatigue (N=33) were included. All patients and controls followed regular school education and were asked to participate after written information. Data of controls were collected at a secondary school in the proximity of Utrecht University Medical Centre. None of the controls had medical involvement for fatigue or sleep complaints.

Methods

Fatigue in the PUF patients in the last 2 weeks was assessed with the subscale subjective fatigue of the validated Dutch version of the self-report questionnaire Checklist Individual Strength (CIS-20). The Checklist Individual Strength-20 (CIS-20) subscale subjective fatigue is a verbal rating scale to express fatigue in 8 different ways with 1 to 7 points and has good reliability and discriminative validity.[17] This scale is used in clinical Chronic Fatigue Syndrome studies.[18]

Controls were asked whether they had serious fatigue complaints during the last month (dichotomously). Sleep quality was assessed in patients and controls by the Sleep Questionnaire (appendix) composed of 5 items on sleep during the previous month. Each item was scored on a 5-point Likert scale. Scores “often” or “always” were regarded as indication for a sleep problem. This short questionnaire offers insight into sleep quality, as perceived by patients and controls. A separate validation study for this questionnaire was not performed. Sleep quantity was assessed by counting the hours of actual sleep. Shortage of sleep was calculated by the difference between the perceived need of sleep hours and the actual sleep hours. Sleep latency was calculated in minutes by the difference between the time going to bed and the time falling asleep.

The medical ethics committee of the University Medical Centre Utrecht approved the study.

Data analysis

Of the variables, group specific means and standard deviations were calculated for descriptive purposes. The data were analysed with linear regression using the variable of interest as dependent variable and a group indicator as independent variable to explore group differences. Results are presented as linear regression coefficients representing the differences between healthy not fatigued and fatigued controls and fatigued controls and PUF patients for the investigated parameter with the corresponding 95% confidence intervals. The same models were used to adjust for age and gender.

Statistical significance was considered by a p-value <0.05.

All analyses were performed using SPSS 14.0 (SPSS, Chicago Il, USA).

Results

The CIS-20 subjective fatigue subscale of the PUF patients was 46.7 (SD 8.8) Likert points. A summary of relevant characteristics of 33 fatigued and 239 non- fatigued healthy controls and their differences is described in table 1, and the characteristics of 82 patients and differences with the 33 fatigued controls in table 2. Between non- fatigued and fatigued controls there were some remarkable differences. The group fatigued controls was older (1.2 (CI 0.6;1.9) year) and contained 16 % more girls. Fatigued controls estimated half an hour more need for sleep (0.5 (CI 0.3;1.0) hour), but slept actually 3 quarters of an hour less (-0.7 (CI -1.1; -0.1) hour), although this difference disappeared in the adjusted analysis. They estimated more hours of sleep shortage (0.6 (CI 0.3;0.9) hours). Moreover, the fatigued controls judged a lower quality of sleep by scoring more sleep problems (1.0 (CI 0.6;1.5) points), particularly light and restless sleep and more daytime naps. In addition fatigued controls also reported more irregularity in sleep habits between school and weekend days. In the weekends they went to bed more than half an hour later (0.6 (CI 0.1;1.1) hour) than non-fatigued controls and seems to compensate sleep shortage more.

Between PUF patients and fatigued controls differences were likewise remarkable. The group patients was younger (-1.3 (CI -1.9;-0.7) year), but also with the same overrepresentation of girls (74 %). They estimated their sleep need almost one hour more (0.9 (CI 0.2;1.5) hour) and slept also actually almost one hour more (0.9 (CI 0.3;1.6) hour), but were as much un-refreshed in the morning. Patients scored more sleep problems (3.0 (CI 1.5;4.5) Likert points), particularly restless sleep and wakes during the nights. They did not report differences between school and weekend nights by going out.

The sleep latency was not significantly different between the 3 groups in the adjusted analysis.

Discussion

Complaints of sleep and fatigue are very common in adolescence. The percentage and gender distribution of healthy controls with fatigue in this study was according to the literature.[4] This study suggests an actual difference in sleeping behaviour between the 3 groups with increasing fatigue. We found the same sleep problems as reported in the CFS literature,[11-16] not only in the PUF patients, but also to a lesser degree in the ‘normal fatigued’ controls. The suggestion of a continuum in sleep problems between not fatigued, fatigued controls and fatigued patients running from no problems to severe problems, does not parallel with the

clear caesura in the sleep quantity between controls and patients. Fatigued controls had the least hours of sleep compared with a non physiological sleep quantity of the PUF patients.
Sleep and waking behaviours of adolescents change significantly from childhood to adulthood. In the second decade of life essential endocrine changes, and psychological and social changes occur. One of the physiological changes is the sleep/wake circadian rhythm conversion from children into an adult rhythm with the development of adult interrelationships of the circadian patterns of bodily functions and increasing resistance against sleepiness.[19-21] This resistance offers a physiological base for later bed times and an increase in evening activities, while the opportunity to sleep is limited by school and practice schedules.[22-25] Increased resistance against sleepiness does not mean a decreased need for sleep. Adolescents need even more sleep than children.[26,27] The later bed times and early school times will lead easily to sleep shortage and the need to compensate in weekends. It is likely that a little sleep shortage is normally in adolescents today. With the onset of adolescence youngsters require 9.2 hours of sleep, but the reality is that they sleep shorter.[28]
The not fatigued controls reported shortage of sleep as well as un-refreshed sleep, but without sleep problems. In the course of adolescence youngsters start with having a night out in weekends till late after midnight and develop more irregularity in their sleep habits. At the same time an increase of the prevalence of fatigue and sleep complaints arises.

Fatigued controls had the most sleep shortage and the most irregularity between week and weekend nights. It seems obvious that fatigue will be the consequence. However, the fatigued controls were not only un-refreshed by sleep shortage, but they also complained significantly more about restless and light sleep and wakes during the night, typical characteristics of less sleep quality.

Sleep shortage and irregular sleep habits challenge the circadian rhythm in an extra delicate adolescent period: the transition to an adult sleeping-waking brain system. This challenge does not only affect the sleep texture, but undermines also the circadian patterns of bodily functions,[29-32] and may result in different somatic complaints and fatigue.[33-35]

At the time of the queries, the duration of sleep was the essential and most striking difference between the 3 groups. Non-fatigued controls slept a little shorter than the estimated need for their age,[28] fatigued controls significantly shorter and PUF patients significantly longer.

The explanation for the long sleep duration in PUF patients is not clear. It might be the result of an increased need for sleep or of less sleep quality, but it might be also the result of a misconception of the real need for sleep by attributions of fatigue to supposed sleep shortage. When sleep is not refreshing, it figures that a longer sleep is needed. However, a sleep duration, that is longer than physiologically necessary, might not restore, but on the contrary maintain a disturbed wake sleep rhythm and circadian patterns.

The present findings lead to two suppositions: In adolescents, changing sleep habits may disturb the circadian rhythm resulting in diminished sleep quality and fatigue, that goes beyond insufficiently rested exercise fatigue and becomes gradually chronic fatigue, and/or the other way round, decreased sleep quality in PUF patients may be a symptom of an otherwise caused disturbed circadian rhythm. So, changing sleep habits may be considered to be one of the predisposing factors for prolonged fatigue, and changing sleep habits, particularly by admitting the increased sleep need, may be considered to be one of the perpetuating factors.

The recognition of the significant place of a disturbed wake / sleep rhythm in fatigue has clinical importance. To prevent a disturbance of a smooth transition to an adult wake / sleep rhythm in healthy adolescents emphasizes the importance of promoting regular sleep habits and discouraging chronic sleep shortage by reconsidering early school schedules.

In chronic fatigue patients, re-establishing the physiological wake / sleep rhythm in stead of giving in to the increased sleep need, may be, in addition to Cognitive Behavioural Therapy and Graded Exercise Therapy,[36,37] one of the key features for recovery.

Appendix

Sleep Questionnaire

(interpreted and completed by patients themselves)

Sleep Problems

How often *never-seldom-sometimes-often-always* (1-5)

Do you wake up un-refreshed?

Do you have a restless sleep?

Do you wake during the night?

Do you have a light sleep?

Do you take daytime naps?

Total score Sleep Problems (5-25)

Sleep-time

Estimated need for sleep (hours)

Actual sleep (hours)

Shortage of sleep (hours)

Sleep latency

Estimated time to fall asleep (minutes)

Table 1:
Characteristics of healthy not fatigued controls and healthy fatigued controls

	fatigued Controls	**non fatigued Controls**	**Difference (CI 95%)**	**P-value**	**Adjusted Difference (CI 95%)**	**P-value**
	N=33	N=239				
Age	15.8 (1.6)	14.6 (1.9)	1.2 (1.9;0.6)	<0.001		
Gender (% female)	70.0	54.0	16.0	0.087		
Estimated need for sleep (hours)	9.0 (1.2)	8.8 (1.4)	0.2 (-0.2;0.7)	0.326	0.5 (0.3;1.0)	0.037
Actual sleep (hours)	7.6 (1.1)	8.3 (1.4)	-0.7 (-1.1;-0.1)	0.023	- 0.1 (-0.6;0.3)	0.574
Sleep shortage (hours)	1.3 (1.1)	0.5 (0.8)	0.8 (0.3;1.1)	<0.001	0.6 (0.3;0.9)	<0.001
Sleep latency (minutes)	34.6 (29.7)	39.4 (29.6)	-4.8 (-15.6;6.0)	0.384	-5.8 (-17.0;5.3)	0.303
Total sleep problems score (5 items 5-25)	11.1 (3.6)	8.2 (2.6)	2.9 (1.6;4.2)	<0.001	2.2 (1.2;3.2)	<0.001
Un-refreshed sleep (1-5)	3.6 (1.3)	2.3 (1.1)	1.3 (0.9;1.7)	<0.001	1.0 (0.6;1.5)	<0.001
Restless sleep (1-5)	2.0 (1.1)	1.5 (0.9)	0.5 (0.1;0.8)	0.006	0.4 (0.0;0.7)	0.025
Wake during night (1-5)	1.8 (0.9)	1.6 (0.8)	0.2 (0.0;0.6)	0.089	0.2 (-0.1;0.5)	0.225
Light sleep (1-5)	2.0 (1.2)	1.5 (0.7)	0.5 (0.2;0.7)	0.027	0.3 (-0.0;0.6)	0.023
Daytime naps (1-5) (number per week)	1.8 (2.0)	1.2 (0.5)	0.6 (0.4;1.0)	<0.001	0.6 (0.2;0.9)	<0.001
Difference week/ weekend actual sleep (hours)	2.9 (1.3)	2.4 (1.2)	0.5 (0.0;0.9)	0.046	0.3 (-0.2;0.7)	0.324
Difference week/weekend bedtime (hours)	2.8 (2.4)	1.8 (1.4)	1.0 (1.5;0.4)	0.001	0.6 (1.1;0.1)	0.029

Adjusted for age and gender

Table 2:
Characteristics of healthy fatigued controls and prolonged unexplained fatigued patients.

	PUF patients	**fatigued Controls**	**Difference (CI 95%)**	**P-value**	**Adjusted Difference (CI 95%)**	**P-value**
	N= 82	N=33				
Age	14.5 (1.5)	15.8 (1.6)	-1.3 (-1.9;-0.7)	<0.001		
Gender (% female)	74.0	70.0	4	0.612		
Estimated need for sleep (hours)	10.2 (1.7)	9.0 (1.2)	1.2 (0.5;1.8)	0.001	0.9 (0.2;1.5)	0.014
Actual sleep (hours)	8.9 (1.7)	7.6 (1.1)	1.3 (0.6;1.7)	<0.001	0.9 (0.3;1.6)	0.008
Sleep shortage (hours)	1.4 (1.5)	1.3 (1.1)	0.1 (-0.4;0.7)	0.657	0.1 (-0.5;0.7)	0.690
Sleep latency (minutes)	51.4 (49.5)	34.6 (29.7)	16.8 (1.7;31.6)	0.029	16.6 (-3.3;36.5)	0.102
Total sleep problems score (5 items 5-25)	13.9 (3.5)	11.1 (3.6)	2.8 (1.4;4.3)	<0.001	3.0 (1.5;4.5)	<0.001
Un-refreshed sleep (1-5)	3.8 (1.0)	3.6 (1.3)	0.2 (-0.3;0.7)	0.402	0.3 (-0.2;0.7)	0.284
Restless sleep (1-5)	2.9 (1.0)	2.0 (1.1)	0.9 (0.5;1.3)	<0.001	0.8 (0.4;1.3)	<0.001
Wake during night (1-5)	2.6 (1.0)	1.8 (0.9)	0.8 (0.4;1.2)	<0.001	0.8 (0.4;1.2	<0.001
Light sleep (1-5)	2.4 (1.1)	2.0 (1.2)	0.4 (-0.0;0.9)	0.051	0.4 (-0.1;0.9)	0.148
Daytime naps (1-5) (number per week)	2.2 (1.2)	1.8 (2.0)	0.4 (-0.2;1.0)	0.214	0.6 (-0.0;1.2)	0.060

Adjusted for age and gender

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Chapter 6

Adverse effects of an educational video film in fatigued children and adolescents: a randomized controlled trial

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Abstract

Background Before fulfilling the CDC criteria for Chronic Fatigue Syndrome children and adolescents will seek medical help, but in a substantial percentage of patients standard management does not prevent an unfavourable development.

Objective To evaluate the efficacy of a video-film intervention in preventing the development of Persistent Fatigue and serious School Absence for children and adolescents aged 8-18 years who have been referred to general paediatrics with unexplained fatigue.

Design Randomised controlled trial

Participants Ninety-one patients referred to a general paediatrician with fatigue; 50 were randomly assigned to receive the intervention (a video film plus usual care) and 41 to standard management only.

Intervention Video film aiming at the education about the diagnosis CFS and the modelling of coping behaviour.

Main outcome measures Self-reported fatigue severity, physical activity, motivation, concentration (Checklist Individual Strength -20 subscale scores) and school absence.

Results 79 patients had completed data at 12 months (42 in the video film group and 37 in the usual care group). Mean fatigue severity and school absenteeism scores did not differ significantly, but in the intervention group the score for reduced motivation was higher (difference 2.9, CI 5.7; 0.1, p=0.038). In addition the intervention group included 18 % more patients with Persistent Fatigue with significant School Absence at 12 months. The odds of developing persistent fatigue and of missing more than 50% of school classes at 12 months was 3.3 times more in the group of patients who had received the video film intervention than in the group of patients who had only received standard management (OR 3.3 (CI 1.0;11.3, p=0.046).

Conclusion This particular video film intervention plus usual care in children and adolescents with medically unexplained fatigue appeared to be inappropriate in preventing an unfavourable development. The intervention even had an adverse effect, i.e. reduced motivation, and increased incidence of the outcome Persistent Fatigue with significant School Absence. Education with this particular video film focussing on the label CFS and on coping strategies, but without actual treatment, is not recommended to young people in the early stage of unexplained fatigue.

Introduction

Prolonged unexplained fatigue is a perplexing problem for paediatricians and patients. It is an important reason for prolonged absence from school with serious implications for education, career and social development. Most fatigue studies focus on Chronic Fatigue Syndrome (CFS), a disorder characterised by persistent medically unexplained fatigue lasting more than 6 months with additional physical symptoms and leading to functional impairments.[1]

Although debate exists among healthcare professionals and patients about appropriate strategies for management of CFS, Cochrane reviews conclude that there is encouraging evidence to show that patients may benefit from graded exercise therapy (GET)[2] and cognitive behaviour therapy (CBT).[3] These reviews include almost exclusively adult CFS studies. Randomised controlled studies in children and adolescents are scarce, but the study of Knoop et al showed that CBT is an effective treatment for CFS in adolescents with positive outcomes sustained for more than 2 years.[4] To the best of our knowledge there are no studies about interventions and management of young patients with debilitating fatigue not fulfilling the CDC criteria for CFS, while a substantial percentage of patients is still persistently fatigued one year later.

Paediatricians are regularly confronted with these patients in daily practice. In a random general population sample of British adolescents 30.3 % reported fatigue, 1.1 % chronic fatigue and 0.5% chronic fatigue syndrome.[5] When these fatigued adolescents seek medical advice and when underlying somatic illnesses and psychological problems are excluded, the clinician will reassure, and in the beginning advise the patient to avoid complete inactivity, engage in moderate level of exercise, and attend school as much as possible. But, this usual care is not always appropriate to prevent an unfavourable development.

Medical reassurance starts with the positive recognition of an illness instead of the mere exclusion of known illnesses. The language that is used by the doctor to attribute the symptoms to a diagnosis is essential in the process of recovery.[6]

In the absence of simple and effective interventions to prevent acute fatigue from becoming chronic for fatigued young people, who are seeking medical care, we developed a video film, focusing on those with the diagnosis Chronic Fatigue Syndrome. The aim of the film was to prevent fatigue becoming chronic in young patients by education about not medical explained fatigue in the earliest stage of their complaints. There are no other films with the same aim in the Netherlands, nor, as far as we know, somewhere else. We made the film to emphasize that their fatigue complaints are real, and to demonstrate how peers with CFS learned to cope with their limitations, and to participate in daily life. In the film young patients with CFS tell their stories. They give insight into the nature of the condition as well as into the way that they cope with it. We hypothesized that, compared to patients randomized to a “care as usual” control group, the patients, randomized to receive the video film plus care as usual, would demonstrate greater reduction in self-reported severity of fatigue and less school absence.

Methods

Participants

Ninety-one patients aged 8 to 18 years, referred for the first time to a general paediatrician with the main symptom of ongoing debilitating fatigue were prospectively included through 2003-2006, after a thorough clinical evaluation (history, physical and laboratory examinations), according to Dutch guidelines by their paediatrician to identify possible underlying or contributing conditions of somatic or psychiatric morbidity. All patients were persistently severely fatigued but did not meet the CDC criteria for CFS[1] due to the brief duration of fatigue (68.3%) and/or lack of additional symptoms. We strictly used, following the Dutch guidelines for young people, in this study the CDC criteria.Thirty paediatricians from 10 different non-academic hospitals, both in smaller and larger towns, collaborated in this study. In the study period of 12 months none of the patients received an alternative diagnosis as an explanation for the fatigue complaints. The usual care by the paediatrician consisted of reassurance and encouragement to attend school as much as possible.

Design and procedures

All patients who met the inclusion criteria (i.e. prolonged unexplained fatigue and aged 8-18 years) were invited by their own paediatrician to take part in this study. Patients and their parents received verbal and written information about the study. If the patients and their legal caregivers gave informed consent for participation in the study, the patient was randomly assigned to one of three intervention conditions (‘care as usual’, ‘video film plus care as usual’ or ‘video film plus the possibility to contact a psychologist plus care as usual’) by means of a sequence, based on a computer-generated list of random numbers. The participants received baseline, three monthly interim and outcome questionnaires, and the video film by mail. The same researcher performed the allocation procedure and data analyses.

Intervention

The video film was developed to present the diagnosis Chronic Fatigue Syndrome, as an explanation for ongoing fatigue, and the treatment options. The film starts with a conversation between two actresses, a fatigued adolescent and her healthy girlfriend, about the impact of fatigue on daily life. Subsequently, three young adolescents with CFS tell their stories about fatigue, the disabilities they had to deal with, and how they learned to cope and find their way to normal life. The film was based upon a script with leading questions and information on treatment approaches, mainly cognitive behavioural strategies. The adolescents told themselves how these strategies supported their recovery. Running through the different scenes, the patients are asked about the recognition of and coping with their own feelings of fatigue.

The intervention is obtainable (in Dutch language) by writing to the first author.

Measurements

Fatigue was assessed with the validated Dutch version of the self-report questionnaire Checklist Individual Strength (CIS). This is a 20-item questionnaire and measures four aspects of fatigue over the most recent 2 week period: fatigue severity (8 items, range 8-56), concentration problems (5 items, range 5-35), reduced motivation (4 items, range 4-28) and reduced activity (3 items, range 3-21). Each item was scored on a 7 point Likert scale. High scores on the subscale subjective fatigue indicate a high level of experienced fatigue and high scores on the concentration, motivation and activity subscales indicate reduced concentration, motivation and activity. The questionnaire has good reliability and discriminative validity.[7]

School absenteeism was measured with a continuous score by the missed classes in the last month divided by the total number of classes in the same period x 100%.

Persistent Fatigue is dichotomously defined as the subjective fatigue severity score above >=40 Likert points, and significant School Absence is dichotomously defined as an absence score was >=50 % of the classes in the last month.

From the start, every 3 months to the end of the study the patients filled out questionnaires by themselves at home and returned them by mail.

The medical ethics committee of the University Medical Centre Utrecht approved this study.

Data Analysis

Because none of the patients took advantage of the opportunity to contact the psychologist (N=16), we decided halfway through the inclusion period to discontinue that particular intervention condition and to classify the patients who received the video film into the same intervention group. Patients randomised after this date were randomised to only two (not three) treatment arms (i.e. “Usual care only” and “”Usual care + video film”). This explains the unequal distribution of patients in both groups (N=50 and N=41).

All analyses were performed using SPSS 14.0 (SPSS, Chicago Il, USA). Significance was assumed at a P value of < 0.05. Of the relevant outcome variables, group means and standard deviations or proportions were calculated for descriptive purposes at baseline and at 12 months follow-up. Outcome measured on a continuous scale was analysed with linear regression using the variable of interest as the dependent variable and a group indicator (treatment as usual =0, treatment as usual plus video film intervention =1) as the independent variable to explore group differences. Results are presented as linear regression coefficients representing mean differences between both groups of patients for the investigated parameter with their corresponding 95% confidence intervals (95%CI). The magnitude of the associations between the dichotomous outcomes of interest and the kind of intervention was quantified by estimating odds ratios (OR) and respective 95% confidence intervals using binary logistic regression, with outcome (yes/no) as the dependent variable and the video film intervention (yes/no) as independent variable.

Results

Ninety-one patients were randomly allocated to either ‘video film plus care as usual’ (n=50) or to ‘care as usual’ (n=41). All patients were Caucasian. At 12 months 79 patients completed the assessment. Twelve patients dropped out during the follow up by not finishing the outcome assessment, in spite of repeated requests. The initial characteristics of interest of the drop outs did not differ significantly from those who completed the study. Nine patients lost to follow were female and 7 of them had been allocated to the usual care plus video film intervention. Table 1 shows the baseline characteristics of both groups. By randomisation both groups did not differ in age, age range, gender, mean school absenteeism, percentage patients with serious School Absence, duration of fatigue complaints or the scores on the 4 different items of the Checklist Individual Strength (CIS-20). The initial characteristics of the patients with the two main outcomes Persistent Fatigue and Persistent Fatigue with significant

School Absence at 12 months did not differ significantly between both groups. Data from questionnaires about school, completed by the same patients, proof school refusal to be unlikely (manuscript in preparation).

Effect of intervention

Tables 2 and 3 show the characteristics at 12 months of 79 patients. Patients in both groups reported no differences in the 3 subscale scores for subjective fatigue, concentration and physical activity, but for the subscale score for motivation they did. The subscale score for reduced motivation was higher in the intervention group than in the ‘care as usual’ group (14.8 (SD 6.3) versus 11.8 (SD 6.2) likert points) (Difference: 2.9 (CI 0.1; 5.7) p=0.038). The incidence of Persistent Fatigue and the mean percentage school absence did not differ significantly between both groups. However, the incidence of the worst outcome - Persistent Fatigue with Significant School Absence - was 18 % higher. In the group of patients with the video film intervention 12 of 22 persistently fatigued patients and in the group of patients with only care as usual 4 of 17 missed more than 50 % of the school classes at 12 months. The odds of becoming persistently fatigued with significant School Absence were 3.3 times more in the video film intervention group (OR 3.3 (CI 1.0:11.3) p=0.046). The proportion of female patients with the worst outcome, was equal to the sex distribution at the moment of randomization (4/5). So far, complete case analyses were conducted. Finally, we attempted to analyse including the cases with partial outcome data. Analysis of the outcomes of the patients of the video intervention group plus the last observations of the missed patients carried forward showed 3.6 (1.0;6.3) (p=0.008)) likert points less motivation, and a 5 times higher risk of becoming persistently fatigued with significant School Absence (OR 5.0 (1.3;19.1) p=0.018).

Discussion

The hypothesis of our study in children and adolescents with prolonged unexplained fatigue was, that labelling the fatigue symptoms as precursors of Chronic Fatigue Syndrome and showing the strategies to cope with the debilitating effects in a video film, might be a good instrument for the general paediatrician to prevent an unfavourable outcome. However, the outcome was contrary to this expectation. The patients who received the video film reported less motivation and a higher incidence of Persistent Fatigue with Significant School Absenteeism. The adverse effects of the intervention might be caused by the double message of the video film. It is possible that patients particularly picked up the first message, (i.e. fatigue complaints may be the result of a well-known condition: Chronic Fatigue Syndrome) as an explanation and legitimization of their fatigue complaints, but the second message (i.e. how to cope successfully with debilitating fatigue and unhelpful thoughts), did not get across. Adolescents might consider the medical label of unexplained symptoms, such as CFS, to be more serious than the same symptoms described using common language.[8] The use of medical labeling can induce bias in perception by increasing the awareness of somatic symptoms, and may result in patients perceiving the condition as a disease.[9] This perceiving may lead to a diminished ability or willingness to engage with normal activities in the face of feeling tired and/or unwell. On the other hand receiving a CFS diagnosis is an intervention in itself, that can bring an end to the burden of uncertainty and might have a positive effect upon fatigue and psychological aspects of well-being, such as more emotional stability and less psychological distress.[10,11] This might promote acceptance of the status quo, but also carries the risk of the symptoms becoming self validating and self-reinforcing.[12] We consider the adverse effects of the video film intervention as the result of these psychological processes, and that interpreting fatigue complaints within the label of CFS encouraged patients to perceive the fatigue as a socially accepted serious entity. Moreover it might have offered a socially sanctioned pathway for CFS illness behaviour such as reduced school attendance and decreased motivation. If this pathway has been appraised as personally relevant, the symptoms offered by the pathway might have been adopted as the forum for communication[13] and may lead to transgression into the sick role and the development of an illness identity.[11] To prevent patients following this pathway, more individual guidance is needed than the education that was offered by the video film.

This study has limitations. The used guidelines for CFS are based on the CDC criteria. The substantial percentage of patients lost to follow up at 12 months, might bias the results. The reason of discontinuation of the follow up was in the first place the lack of willingness to complete anymore questionnaires, and not recovery. The lost to follow-up group had the same initial characteristics as the other patients. Analysis of the last observations carried forward showed the same outcome.

So, we conclude that this particular video film intervention with the intention to inform about the diagnosis CFS and to coping behaviour, is not appropriate to prevent an unfavourable development in fatigued children and adolescents. The intervention even carries the risk of reinforcement of symptoms and legitimization of functional disabilities with less motivation and less school-attendance.

This conclusion is a serious warning against medicalization by assigning the label of CFS without an adequate intervention to children and adolescents in the early stage of Prolonged Unexplained Fatigue. This video education / modelling film cannot be replaced by personal education about the bio-psycho-social aspects of fatigue and personal support in coping with limitations.

Table 1: At baseline: Characteristics of patients and differences between intervention groups. Values are means (SD) or percentages

	Patients N=91	
Demography	**Usual care + Video film; yes; N=50**	**Usual care only; N=41**
Age (years)	14.1 (1.7)	13.7 (2.4)
Female gender (%)	78.0 N=39	65.9 N=27
Fatigue		
Duration of complaints (months)	7.1 (5.3)	5.9 (3.8)
Score Checklist individual strength (20 items, range 20-140)	95.8 (20.5)	96.9 (17.9)
Score subscale subjective fatigue (8 items, range 8-56)	46.6 (8.8)	46.7 (9.1)
Score subscale concentration (5 items, range 5-35)	21.2 (9.4)	22.6 (7.8)
Score subscale motivation (4 items, range 4-28)	17.2 (6.0)	15.4 (5.7)
Score subscale physical activity (3 items, range 3-21)	13.4 (4.7)	12.7 (5.3)
School		
School Absence (%)	50.5 (46.1)	50.2 (45.1)
Number (%) of patients with significant School Absence (> 50%) (y/n)	N=23 (46.0)	N=18 (43.9)

Table 2: At 12 months: CIS-20 with subscale scores and school attendance of patients and differences between intervention groups Values are means (SD) or percentages

	Usual care + Video film; N=42	**Usual care only; N=37**	**Difference (95% CI)**	**p-value**
Score Checklist individual strength (20 items, range 20-140)	79.9 (31.8)	77.8 (23.0)	2.1 (14.7;-10.5)	0.741
Score subscale subjective fatigue(8 items, range 8-56)	35.8 (15.9)	36.3 (12.0)	-0.5 (5.9 ;-6.9)	0.872
Score subscale concentration (5 items, range 5-35)	19.8 (9.5)	19.9 (7.5)	0.1 (3.8;-4.0)	0.954
Score subscale motivation (4 items, range 4-28)	14.8 (6.3)	11.8 (6.2)	2.9 (5.7;0.1)	0.038
Score subscale physical activity (3 items, range 3-21)	10.7 (5.6))	10.7 (4.9)	0.0 (2.3;-2.4)	0.976
School Absence (%)	21,3 (29.4)	16.9 (31.8)	4.4 (18.7:-10.0)	0.544

Table 3: At 12 months: Odds ratios for association between interventions and Persistent fatigue and Persistent Fatigue with Significant School Absence.

	Usual care + Video film N=42	**Usual care only N=37**	**Odds Ratio (95% CI)**	**p-value**
Persistent Fatigue** (0-100%)	N=22 (52.4%)	N=17 (45.9%)	1.7 (0.7 ;4.0)	0.208
Persistent Fatigue** with Significant School Absence* (% y/n)	N=12 (28.8%)	N=4 (10.8%)	3.3 (1.0;11.3)	0.046

* Significant School Absence when school absence >50 %.

** Persistent Fatigue when subjective fatigue subscale >= 40 likert points

Appendix

Consort Flow Diagram

Assessed for eligibility
N=97

Excluded
N=6

Reasons for not participating in RTC: 4 no willingness and 2 too late for inclusion

Randomised
N=91

Allocated to intervention	**Allocated to intervention**
“Usual care + video film	“Usual care only”
N=50	N=41
Female N=39	Female N= 27
Male N=11	Male N=14

Lost to follow up at 3 months	**Lost to follow up at 3 months**
N=6	N=2
Female N= 4	Female N=1
Male N=2	Male N=1

Reasons for discontinued intervention: no willingness anymore to complete questionnaires

Lost to follow up at 6 months	**Lost to follow up at 6 months**
N=3	N=1
Female N= 3	Female N=1
Male N= 0	Male N=0

Analysed at 6 months	**Analysed at 6 months**
N=42	N=37
Female N= 33	Female N=24
Male N=9	Male N=13

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Chapter 7

Adolescent Chronic Fatigue Syndrome: A Follow-up Study

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Abstract

Objective To describe the symptomatic and educational long-term outcome, healthcare use, and risk factors for non-recovery in adolescent chronic fatigue syndrome (CFS).

Patients and Methods 60 adolescents, diagnosed in accordance to the US Centers for Disease Control and Prevention criteria for CFS, were followed up at a mean of 2.2 years (SD, 1.6) after initial assessment. The subjective fatigue subscale of the Checklist Individual Strength (CIS-20) and physical role functioning subscale of the Child Health Questionnaire (CHQ-CF87) were used as primary outcome measures. On these measures, cut-off scores for improvement were specified. A general questionnaire regarding additional symptoms, school attendance, work attendance and treatment, was also applied.

Results Complete measurements for 54 adolescents were returned (90%). At initial assessment, their mean age was 16.0 years (SD, 1.5), and 20.4% was male. At follow-up, the mean age was 18.2 (SD, 1.5), 28 (51.9%) adolescents had a near to complete improvement, but 26 (48.1%) were not improved. Those teenagers who attended school (n, 41) had missed an average of 33% of classes during the last month. The rest (n, 13) had worked an average of 38.7% of a fulltime job during the last month. 66.7% of the subjects had been treated by a physiotherapist, 38.9% were clinically treated in rehabilitation, 48.1% had received psychological support, and 53.7% had made use of alternative treatment.

Conclusion About half of the adolescents had recovered from CFS at follow-up. The other half was still severely fatigued and physically impaired. Health care use had been high, and school- and work attendance was considerably lower than in healthy adolescents. Older age at inclusion was a risk factor, and pain, poor mental health, self-esteem, and general health perception at outcome, were associated with an unfavorable outcome. Future research should focus on customizing existing treatment and studying additional intervention options.

Introduction

The chronic fatigue syndrome (CFS) in adolescence is a heterogeneous and medically unexplained condition.[1] No laboratory tests for (adolescent) CFS are available.[2] Its main symptom is functionally disabling fatigue, severely affecting (young) patients' lives.[3] Like in adult CFS, the most commonly used criteria in adolescent CFS are the English Oxford,[4] and the US Centers for Disease Control and Prevention (CDC)[5] criteria. The Oxford criteria are generally considered somewhat less restrictive.[6] The prevalence of adolescent CFS has been estimated at 1.3-4.4% in British and US populations.[7,8] Estimations of the prevalence of adolescent CFS in the Dutch population are lower.[9] The incidence of adolescent CFS is estimated at 0.5%,[10] and the female to male ratio is estimated at 4:1.[11] Randomized controlled treatment trials for adolescent CFS have been rare, but there is growing support for a positive effect of cognitive behavior therapy.[12,13]

There have only been a few follow-up studies describing the outcome of adolescent CFS after regular care, applying either Oxford, or CDC-criteria for CFS. In table 1, the main studies on the prognosis of adolescent CFS are presented. About one-third, to a half of the patients in the presented studies still experienced severe fatigue, physical impairment and little improvement at follow-up. At present, the largest cohort described in a follow-up study of pediatric CFS included 35 patients. Most studies so far have used the Oxford criteria for CFS, and there is only one follow-up study that has employed the CDC (1994) criteria for CFS. However, all diagnoses in these studies were made retrospectively. Furthermore, most studies had a disproportionately high percentage of male participants and a wide age range. In this study, the outcome of 54 adolescents, fulfilling the CDC (1994) criteria for CFS is described.

Methode

Participants

The participating adolescents had first visited a general practitioner before being referred to a general pediatrician in a non-academic setting. Subsequently, they were referred to the University Medical Center Utrecht, The Netherlands. 74 adolescents who had previously participated in a number of research studies into adolescent CFS[21,22] were considered for inclusion. At initial examination, these adolescents were assessed for CFS and the diagnosis, in accordance with the CDC-1994 criteria, was either made or confirmed by a specialized academic pediatrician. Although they had been clinically diagnosed with CFS, 14 of the 74 adolescents (18.9%) were not eligible for participation in this follow-up study because their initial scores on the subjective fatigue subscale of the Checklist Individual Strength (CIS-20) were below cut-off (see next section). Questionnaires were sent to the remaining 60 adolescents. All questionnaires were filled out at home. The duration of the follow-up was defined as the time between the initial research examinations at the University Medical Center, and the present study's assessments. The study was approved by the ethical committee of the University Medical Center, and informed consent was obtained from all participating adolescents and their parents.

Primary outcome measures

Fatigue was assessed with the subjective fatigue subscale of the CIS-20[23]. This scale measures experienced fatigue, and consists of 8 items; scores range from 8 (no fatigue) to 56 (extremely fatigued). It is a reliable, validated assessment measure, with good internal consistency (Cronbach's α 0.93[12]). The CIS-20 has previously been used in research into adolescent CFS.[22] Various cut-off scores (ranging from 35.7-40) for recovery on this measure have been employed.[24,12] In this study the cut-off on this subscale was set at 40 (mean, plus 2 SD of the subjective fatigue distribution in healthy adolescents),[24] to dichotomize outcome as improved (<40) or not-improved (≥40).

Functional impairment was measured with the physical role functioning subscale of the Child Health Questionnaire-Child Form (CHQ-CF87).[25] This scale measures limitations in school work and daily activities as a result of physical health, and consists of 3 items; scores range from 0 (severe limitations, due to physical problems) to 100 (no limitations, due to physical problems). It is a reliable, validated assessment measure, with good internal consistency (Cronbach's α 0.86[26]). The CHQ-CF87 has previously been used in research into adolescent CFS[23]. Cut-off scores for recovery on the physical role functioning subscale of the CHQ-CF87 have not yet been set for adolescent CFS. However, on the physical functioning subscale of the Short-Form General Health Survey (SF-36),[27] also ranging from 0 (maximal physical limitation) to 100 (ability to do all activities) and previously employed in adolescent CFS, a cut-off of 65 has been used.[12] In this study, the cut-off on the physical role functioning subscale of the CHQ-CF87 was correspondingly set at 65, to dichotomize outcome as improved (>65) or not-improved (≤65). A classification of near to complete improvement required a score <40 on the subjective fatigue subscale of the CIS-20, combined with a score >65 on the physical role functioning subscale of the CHQ-CF87.

Secondary outcome measures

In addition to the physical role functioning subscale of the CHQ-CF87, we employed the emotional role functioning subscale, measuring limitations in school work and daily activities as a result of emotional problems, such as worry or sorrow (Cronbach's α 0.90[26]), the behavioral role functioning subscale, measuring limitations in school work and daily activities as a result of behavioral problems (Cronbach's α 0.71[26]), the bodily pain subscale, measuring severity and frequency of bodily pain (Cronbach's α 0.85[26]), the general behavior subscale, measuring the exhibition of aggressive, delinquent and immature behavior (Cronbach's α 0.79[26]), the mental health subscale, measuring a diversity of positive and negative feelings (Cronbach's α 0.86[26]), the self-esteem subscale, measuring satisfaction with abilities, looks, family/ peer relations and life overall (Cronbach's α 0.89[26]), and the general health perceptions subscale, measuring believes concerning health (Cronbach's α 0.77[26]), in order to cover additional physical and psychosocial domains at outcome.

In a general questionnaire, the participants were asked to indicate (yes/ no) the regular presence during the last month of 8 symptoms in accordance to the CDC-1994 criteria (self-reported impairment in memory or concentration, sore throat, tender cervical or lymph nodes, muscle pain, multi-joint pain, headache, unrefreshing sleep, post-exertional malaise lasting 24h or more). School attendance was measured by dividing the attended school classes by the total number of scheduled classes in the past four weeks. If the participants no longer attended school, work attendance was calculated as the percentage of a fulltime job (38h) the adolescent had worked during the last month. Finally, participants were asked to estimate the total number of therapeutic visits they had (if any) with physiotherapists, psychologists and alternative healthcare suppliers in the follow-up period, and (if applicable) to estimate the months they had spend in clinical rehabilitation.

Analyses

All statistical analyses were performed using SPSS (version 16.0). On the outcome variables, group means and standard deviations were calculated. Potential risk factors (e.g. gender, age, severity of fatigue at inclusion, duration of follow-up) were quantified through odds ratios using logistic regression with outcome (recovered/ not recovered) as dependent variable. The significance level was set at $P<.05$ (two-tailed tests).

Results

Complete data for 54 (90%) adolescents were returned. At first inclusion, their mean age was 16.0 years (SD, 1.5), all were Caucasian, 20.4% was male, and their mean score on the subjective fatigue subscale of the CIS-20 was 49.4 (SD, 5.1). The onset had been gradual in 27 (50%) of the cases, following 'flu-like illness' in 22 (40.7%) of the cases, and 'acute' in 5 (9.3%) of the cases. At follow-up, the mean age was 18.2 years (SD, 1.5). There were no significant differences between responders and non-responders in gender, age or fatigue severity. The mean follow-up duration was 2.2 years (SD, 1.6), but the symptoms in most cases had existed substantially in the years prior to initial assessment. During follow-up, 43 (79.6%) adolescents had not received any other diagnoses. 11 (21.4%) adolescents received another diagnosis that not fully explained the invalidating fatigue (after treatment); 3 (5.6%) were diagnosed with celiac disease, 3 (5.6%) with lactose intolerance, 2 (3.7%) with metabolic disorder, 1 (1.9%) with hypermobility syndrome, 1 (1.9%) with major depressive disorder, and 1 (1.9%) with anxiety disorder.

Table 2 shows the scores on the primary outcome measures of the 54 adolescents for whom complete measurements were returned. At follow-up, 28 adolescents (51.9%) had a score <40 on the subjective fatigue subscale of the CIS-20, and a score >65 on the physical role functioning subscale of the CHQ-CF87, indicating that they had a near to complete improvement from CFS at follow-up.

Table 3 shows the scores on the secondary outcome measures. The mean scores on the behavioral role functioning, the emotional role functioning, and the general behavior subscales of the CHQ-CF87 were generally good. However, the mean scores on the mental health and self esteem subscales of the CHQ-CF87 were unfavorable (approximately 1 SD below the mean scores in a healthy young population[26]), and especially the mean scores on the bodily pain and general health perceptions subscales of the CHQ-CF87 were low (respectively about 1.5 and 2 SD below the mean scores in a healthy young population[26]).

Table 4 shows the school attendance, work attendance and therapeutic contacts of the 54 adolescents for whom complete measurements were returned. At follow-up, the participants who attended high school or college had on average missed approximately one-third of the regular classes during the last month. For a previously described cohort of 167 healthy adolescents, surveyed in the same way, this percentage was only 12.5%[21]. Those participants who no longer attended school had worked only an average of approximately one-third of a fulltime job during the last month. Of these, 3 (23.1%) adolescents indicated that it was their choice to work part-time, but for the other 10 (76.9%) it was due to the CFS symptoms. The variety and frequency of therapeutic healthcare use had been considerable between initial assessment and follow-up.

Only a higher age at initial inclusion was found to be a risk factor for non-recovery of CFS at follow-up (odds ratio, 1.59; 95% CI, 1.06-2.39; *P*=.03). Gender, severity of fatigue at inclusion, type of onset, other diagnoses, health care use (psychological treatment, physiotherapy, rehabilitation or alternative treatment), and length of time between inclusion and follow-up were not associated with outcome. At follow-up, a high amount of reported CDC CFS-symptoms (odds ratio, 1.62; 95% CI, 1.19-2.22; *P*=0.00), and a low score on the mental health (odds ratio, 0.95; 95% CI, 0.90-0.99; *P*=.01), self esteem (odds ratio, 0.94; 95% CI, 0.90-0.99; *P*=.01), bodily pain (odds ratio, 0.93; 95%CI, 0.93-0.99; *P*=.00), and general health perceptions (odds ratio, 0.92; 95% CI, 0.84-0.96; *P*=0.00) subscales of the CHQ-CF87 were associated with non-recovery.

Discussion

The outcome of unexplained pediatric chronic fatigue (i.e. not diagnosed as CFS) is mostly positive.[28,29] It is generally thought that the prognosis for adolescent CFS is also relatively good.[1,2] In this study it was found that, although about half of the participating adolescents had a near to complete improvement, the other half was still severely fatigued, had impaired physical functioning, and would probably still fulfill CDC-1994 criteria for CFS at follow-up. The cohort of adolescents participating in this study is the largest described in any follow-up after regular care. The diagnosis of CFS was established according to the CDC-1994 criteria at initial examination, the female to male ratio was in accordance with research findings, the mean age of participants did not have a wide range, and a strict cut-off score, on a validated measure for adolescent CFS, was used to qualify subjects for inclusion. However, the CHQ-CF87 was not employed at inclusion. Therefore, potential predictors for outcome were limited. Furthermore, the home completion of questionnaires might not ensure complete confidentiality without parental influence, and the self-report of healthcare use and work- and school non-attendance might not be completely accurate.

In previous studies, few risk factors for (adolescent) CFS have been identified.[30] Like in our study, an older age at diagnosis has been found to imply an increased risk for prolonged adolescent CFS.[3,10] The high levels of school non-attendance are in concordance with the literature.[31,1,2] The use of health care services in adolescent CFS was high and also comparable to recent studies.[32,33] Although some of the participating adolescents had received CBT as part of psychological support, this did not influence outcome. The percentage of adolescents who had not recovered from CFS at follow-up in this study was somewhat higher than in the previous studies and more like the outcome rates in adult CFS.[34] This might be due to the strict use of CDC-1994 criteria for CFS, the employment of a cut-off score for eligibility, and a higher age of participants at inclusion. In addition, the diagnosis of CFS in the adolescents participating in this study was established (or confirmed) in a tertiary, academic hospital setting and might represent a particularly impaired cohort.

Despite intensive health care use a substantial proportion of adolescent patients with CFS remain severely fatigued and physically impaired. This is associated with considerable bodily pain, poor mental health, self esteem and general health, and impacts greatly on school- and work attendance. Therefore, future research into adolescent CFS should not only focus on recognizing patient characteristics for a favorable outcome, but should also be directed towards further customizing existing treatment, and studying additional interventions for those patients that do not benefit from established treatment options.[35,36]

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Table 1: Follow-up studies of adolescent CFS

Study	n[a]	Age[b]	Gender[c]	Duration[d]	Criteria[e]	Outcome
Smith et al. (1991)[14]	15[*] (100%)	14.5 (1.7)	40%	1.1-2.7	CDC (1988)[†]	26.7% recovered from illness; 26.7% marked improvement; 46.7% unimproved or worse.
Rangel et al. (2000)[16]	25 (78.1%)	11.7 (2.2)	40%	3.8	Oxford[†]	36% recovered; 32% mildly fatigued and impaired; 32% unimproved or worse.
Bell et al. (2001)[17]	35[**] (76%)	12.1 (5-18)	31.4%	13.0	Patients diagnosed before 1988[†]	37.1% recovered from illness; 42.9% better, but not resolved; 11.4% chronically ill; 8.6% more ill.
Gill et al. (2004)[18]	16 (72%)	14.9 (2.4)	25%	4.1	CDC[†]	25% near to complete improvement; 31% partial improvement; 44% unimproved or worse.
Sankey et al. (2006)[20]	28 (60%)	13.3 (7-17)	54%	3.0	Oxford[†]	66.7% improved; 33.3% unimproved or worse.

Note. Table might not include all research on the outcome in adolescent CFS (according to the Oxford, or the CDC-criteria), but to the authors' best knowledge represents the main studies in the field. [a]Number of participants (response rate, %). [b]Age at onset in years (SD; otherwise range). [c]Percentage of male participants (%). [d]Duration of follow-up; mean in years (SD; otherwise range). [e]Diagnostic criteria used in study. [*]5 subjects were also identified with major depression (including some who were also diagnosed with CFS), the respondent was either the adolescent or the adolescent's parent, and eventually only six patients fulfilled CDC (1988) criteria for CFS [**]Patients were part of a cluster outbreak of CFS, and authors' own CFS-criteria were used[18]. [†]Diagnosis established retrospectively.

Table 2: Primary outcome measures

	Mean (SD)	*Number of patients below (CIS-20), or above (CHQ-CF87) cut-off n (%)*
Checklist Individual Strength (CIS-20)[a]		
Subjective fatigue	34.3 (14.1)	30 (55.6%)[*]
Child Health Questionnaire (CHQ-CF87)[b]		
Role functioning: Physical (3 items; 0-100)	71.9 (28.3)	38 (70.4%)[**]
Near to complete improvement, n (%) [c]	- --	28 (51.9%)[***]

Note. [a]Score ranges from 8-56; a high score indicates a high level of fatigue. [b]Score ranges from 0-100; a high score indicates better physical functioning. [c]Primary outcome measure. *Score <40 [**]Score ≥65 [***]Subjective fatigue subscale (CIS-20) <40, and physical role functioning subscale (CHQ-87) >65.

Table 3: Secondary outcome measures

	Mean (SD)	*Number of patients above (CHQ-CF87), or below (CDC-criteria) cut-off n (%)*
Child Health Questionnaire (CHQ-CF87)[a]		
Role functioning: Emotional (3 items; 0-100)	84.9 (25.2)	46 (85.1%)*
Role functioning: Behavioral (3 items; 0-100)	95.8 (10.5)	52 (96.3%)*
Bodily pain (2 items; 0-100)	56.1 (27.9)	22 (40.7%)*
General behavior(16 items; 0-100)	82.0 (10.7)	49 (90.7%)*
Mental health (16 items; 0-100)	68.8 (14.9)	34 (63.0%)*
Self esteem (14 items; 0-100)	66.2 (14.6)	28 (51.9%)*
General health perceptions (13 items; 0-100)	46.8 (18.7)	10 (18.5%)*
CDC-criteria[b]		
Additional symptoms	3.8 (2.3)	20 (37%)**

Note. [a]Scores range from 0-100; higher scores indicate more well-being. [b]Score ranges from 0-8; a high score indicates more symptoms in accordance with CDC-1994 criteria. *Score ≥65 **Score <4

Table 4: School attendance, work attendance and health care use at follow-up

School attendance and work	
Adolescents attending school*, n (%)	41 (75.9%)
Percentage of classes followed, % (SD)	67.0% (34.2)
Adolescents working**, n (%)	13 (24.1%)
Percentage of full-time job worked***, % (SD)	38.7% (35.0)

Health care use	
Physiotherapy, n (%)	36 (66.7%)
Mean number of contacts (SD)	45.9 (46.6)
Alternative treatment, n (%)	29 (53.7%)
Mean number of contacts (SD)	16.8 (15.5)
Psychological support****, n (%)	26 (48.1%)
Mean number of contacts (SD)	32.6 (32.6)
Clinical treatment in rehabilitation, n (%)	21 (38.9%)
Mean months in treatment (SD)	3.6 (2.2)

Note. *32 (78%) adolescents attended high school and 9 (22%) adolescents were in college **Only those adolescents no longer attending school. ***38 hours per week. ****General non-CFS specific CBT was applied as psychological treatment

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Chapter 8

General discussion

General discussion

We studied Prolonged Unexplained Fatigue in a group of patients from 8 to18 years with a focus on characteristics, course of fatigue, prognostic factors for prolonged fatigue, sleep quality and efficacy of a video film intervention. Furthermore a follow up study in adolescents with Chronic Fatigue Syndrome was performed. In this final chapter, the results of these studies will be discussed, recommendations for the daily paediatric practice presented, and ideas for future research put forward.

Prolonged Unexplained Fatigue in children and adolescents is a condition with a serious risk for their educational and social development. It is also a great challenge for the paediatrician. When prolonged fatigue evolves towards the Chronic Fatigue Syndrome, it diminishes the possibilities for a satisfactory adult life.[1-3]

Diagnostics

When the general paediatrician is confronted with a patient with ongoing fatigue, and there is no straight-away explanation for the complaints, the paediatrician has to decide how many diagnostic procedures have to be done in excluding all relevant pathology. The risk of unnecessary examinations, often urgently requested at every visit by the patient or the parents to be continued, is real. However unnecessary examinations are not harmless, as they may emphasize the possibility of a serious underlying condition as an explanation for the fatigue. Furthermore, the longer the diagnostic process, the later the treatment will be. This will frustrate patient, parents and paediatrician,[4,5] and finally may lead to 'medical shopping' either in regular or in alternative medicine. For basic treatment, directed at the prevention of school absenteeism and of social isolation, it is important that the period of examinations will be as short as possible and will be concluded with a clear message of no relevant pathology. The longer the fatigue exists, the less favourable the prognosis will be.[6,7] The diagnosis PUF and CFS are diagnoses by exclusion. There are no specific tests for fatigue. Paediatricians need guidelines for diagnostic procedures and the presentation of a trustworthy explanation for the fatigue as the start of treatment. In the paediatric setting a short standard battery of laboratory tests is adequate to exclude somatic pathology. Further examinations are only necessary on indication dependent on 'red flags' in history, physical examination and laboratory test results.[8-10]

An explanatory framework for trustworthy Prolonged Unexplained Fatigue

As said in the general introduction, the diagnosis ‘Chronic Fatigue’ has the negative connotation of ‘never ending’ and we recommend the use of the neutral diagnosis ‘Prolonged Unexplained Fatigue (PUF)’ or in Dutch, ‘Aanhoudende Onverklaarde Moeheid (AOM)’. We described the hypothesis, that this fatigue could be a prominent symptom of a disturbed equilibrium within the network of psycho-neuro-immuno-endocrine systems. To explain the disturbance to the patient and parents, the use of a metaphor may be helpful.

The metaphor of the symphonic orchestra

The orchestra is the metaphor for the network,
the separate groups of instruments for the separate systems,
the harmony between the different instruments for the fine tuning of the different systems on each other.

The orchestra was playing well, almost automatically, and without important interventions of the conductor. However, a certain accident from outside or inside the orchestra disturbed the harmony in the music for a moment. Thereupon the separate instruments started to try to restore the harmony, separately and without taking notice of the conductor, but with the consequence of disharmony. The accident itself may be have gone and forgotten, but as long as the separate instruments do not correct each other, and do not follow the conductor, the disharmony will go on.

Opmerking [H.W.1]: dit met grijd raster o.i.d. weergeven

The patient finds himself in a corresponding situation. As long as one or more systems of the network have not been calmed down, the equilibrium will remain disturbed. The patient has to become his own conductor by taking direction, without lending his ears too much to the somatic symptoms.

The Fatigue Continuum

The diagnosis of Chronic Fatigue Syndrome (CFS) for patients with ongoing fatigue is based on an addition of mainly subjective criteria.[11] Essential in the criteria is the criterion of 6 months duration of fatigue, although this is under debate in the UK.[16] CFS is the extreme of a continuum of fatigue.[12,13] The category of assigning the diagnosis CFS is useful for the recognition of an illness and the possibility of start of a treatment. Furthermore the category CFS is useful for scientific research purposes as it is the only possibility to get more homogeneous study-populations. The daily clinical practice is quite different. All CFS patients begin by definition with fatigue without fulfilling the criteria, and many of them visit the paediatrician in an early stage. The population of fatigued patients without a medical or psychological explanation is heterogeneous.[14,15] We use the diagnosis PUF for those patients, who do not fulfil the CDC criteria for CFS. Because all CFS patients have been PUF patients, but not all PUF patients will develop CFS, the paediatrician is confronted with the dilemma who needs special CFS treatment programs, and who reassurance and advices only. As shown in chapter 3, half of the PUF patients will recover without special treatment. In chapter 2, we found that the severity of fatigue and other somatic complaints of PUF patients corresponded with the complaints of CFS patients, and that particularly the time criterion is the most discriminating factor. That may support the proposal to broaden the CFS definition for paediatric use to the duration of 3 months.[16] However, in such a definition half of the PUF patients should have to undergo an unnecessary treatment. That is not only expensive, but may overshoot the goal of the treatment, as we showed in chapter 6. We found indications that the suggestion to PUF patients, that their fatigue is corresponding with the fatigue of CFS, resulted in illness behaviour with more school absence and less motivation.

Prognosis

PUF patients do not form a homogeneous group. The course of fatigue differed strongly. In half of the patients the fatigue severity diminished, particularly in the first 3 months, but in the other 50 % there was a development into a chronic fatigue syndrome, and half of the patients with CFS had more than 3 years later, still CFS. This means that the risk for an early fatigued youngster, who visits the paediatrician for the first time, to remain severe fatigued 4 years later is roughly 25%. This underlines the seriousness of unexplained fatigue in youngsters and the need for possibilities to distinguish patients with better and a worse prognoses in the early stage of the illness. In chapter 3 we described some prognostic risk- and protective factors for the development of prolonged unexplained fatigue, when the patient visits the paediatrician for the first time. Some patients had somatic symptoms probably connected to autonomic dysregulation, and particularly these symptoms were predictive for the persistence of fatigue. Furthermore, also a physical inactive lifestyle preceding the onset of fatigue and sleep problems at the time of referral were risk factors. Knowing these different prognostic factors allows the paediatrician to fit a more ‘patient-tailored therapy.’

Characteristics

There exist big differences between the prevalences of the severe fatigued youngsters in the population, of the patients who are seeking help at their general practitioner, and of the patients, who are referred to a paediatrician.[56-59] The differences may be explained by the disabling effects of the fatigue or attributions by the patients and or their parents. It does not seem to be the severity of the fatigue itself, which makes the distinction, because established by a questionnaire like CIS-20 fatigue looks similar severe. We investigated some characteristics of the patients referred by their general practitioner to paediatrics and found a likeness with CFS patients.[17] In the first place they all were born in original Dutch families. They had, corresponding with CFS patients, a similar presence of different somatic complaints and sleep problems. Preceding the onset of fatigue their lifestyle was characterized by less physical activities in sports clubs and social embedded activities, but more active in sedentary hobbies like television, computer and particularly cultural hobbies. Following the idea, that regular physical activities are needed for some one's health and well being, the absence of these activities might be regarded as a contribution to the onset of fatigue. But it is also possible, that those who are vulnerable for PUF have viewer inclinations for physical activities and develop quite different leisure activities. These inclinations and the vulnerability for PUF might be coupled phenomena, and when these youngsters urge themselves to be more physical active, there might be a bigger risk of 'over-activity'. As has been shown in adults, an 'overactive' lifestyle can predispose to CFS.[38] In this study, some of the most severe fatigued patients reported solo sports activities far above the average. Their fatigue could be the result of an underlying vulnerable physical condition or not balanced exercises. We found an aggregation of fatigue in families. That suggests that the vulnerability might be caused by genetic transfer or family environment interaction,[18] but at young age, environmental factors determine more than genetic factors.[19-21]

The patients are students in average higher level schools and report to have had no school problems before the onset of fatigue. They estimate their relationships with peers and teachers as good. These answers may be 'rose coloured' and biased by the time, but offer an impression of how they see themselves at the moment of referral. Their parents are higher educated and particularly their fathers worked more hours a week than corresponding fathers. More than half of the patients reported serious life events in the past year. It is not clear whether that differs from the peers group, but it is known that life events may be predisposing factors.[60]

The characteristics of the patients and their families may not be interpreted as causal associations with the fatigue. It might be more likely that they are associated with medical help seeking behaviour and decisions for referral by general practitioners to paediatrics.

Sleep and fatigue

Sleep and fatigue are apparently connected phenomena. Fatigue will commonly resolve by rest during sleep. Unrefreshed sleep is a key symptom in the definition of CFS.[11] However, unrefreshed sleep is also a common complaint in patients with PUF and even in fatigued healthy controls, and is thereby not a discriminating symptom for CFS. We described in chapter 5 besides the unrefreshed sleep more elaborated sleep problems and found increasing problems with increasing debilitating fatigue. The higher score on sleep problems may be seen as less sleep quality. This is in contrast to studies on adult patients with CFS, who had little or no objective indications for sleep.[22—24] It is possible that the expectation of the 'fatigue resolving potency' of sleep is a bias for the interpretation of the quality afterwards and that the feeling of not to be refreshed colours this interpretation. However, the finding that subjective sleep quality decreased from non-fatigued healthy controls via fatigued healthy controls to PUF patients, suggests a sleep quality continuum related to debilitating fatigue.
We also described a relation between the sleep quality and the deviations from the average for age-related sleep habits in both fatigued groups, but in the opposite direction. Fatigued patients clearly slept more hours a night and more regularly; fatigued youngsters from the control group slept shorter and with more irregularities between weekend and schooldays. So, there was, besides the continuum of sleep quality, a clear caesura in sleep quantity between controls and fatigued patients.

Following the hypothesis, as mentioned in the general introduction, that ongoing fatigue is a symptom of a disturbance of the homeostasis of the psycho-neuro-immuno-endocrine network, and that the circadian rhythm has a central control in that equilibrium,[25-28] disruptions of the circadian rhythm will not remain without consequences for the network.[29,30] But, the other way round, disturbance of the homeostasis of the network will have consequences for the circadian rhythm, and thereby on sleep.[31,32] That is why many diseases are accompanied by sleep problems, PUF not excluded. So, on the one hand, it is likely that sleep problems are not the cause of fatigue, but rather a joint symptom of the disturbed homeostasis, while, on the other hand sleep shortage and irregularity in sleep habits may be the origins of disturbance of the circadian rhythm and by that of the homeostasis.

The transition to an adult sleep / wake circadian rhythm makes adolescence, with the many physical and endocrine changes, to a vulnerable period in human life for deregulations of the inner homeostasis.[33] Sleep shortage and irregular sleep habits, particularly for some extra vulnerable youngsters, may be too much to allow a smooth transition. The less sleep quality in fatigued controls might be the result of the sleep habits, leading to a disturbed homeostasis. In patients, the other way round, the disturbance can be caused and maintained by quite different factors. To prevent the disturbance of the circadian rhythm, sleep hygiene is for youngsters a useful advice. However, real life of the adolescent does not stop at nine o'clock in the evening, while the school bell rings early in the morning.

A few studies report better school results after allowing a later start of school.[34,35] It might be valuable to do additional research on sleep quality and fatigue in adolescents who start at school one hour later.

Physical exercises in sports and fatigue

In modern western countries, playing sports is an important leisure activity in youth and almost the only form of physical exercise. In chapter 3 we reported that previous physical inactivity predicted for a negative outcome in PUF patients. In adult studies the effect of sports activities on the prevalence of CFS is not univocal.[36-38] CFS in adults is associated with (too) little as well as (too) much physical sports exercises. In athletes the Overtraining Syndrome is a known condition of increasing fatigue and decreasing performance capacity.[39,40]

In chapter 4, different kinds of sports activities were described, and it turned out that previous exercises in sports clubs predicted a favourable course of fatigue, but self-regulated exercises did not. Patients with PUF with an extreme amount of self-regulated exercises even showed the worst outcome, but their number was too small for definitive conclusions.

There are essential differences between self-regulated and sports club exercises. Exercises in sports club are mostly regular and structured with attention to one's physiologic limits. The training and competition are embedded in a social structure with peers. It is not as much the time spent on exercise, but the membership itself of a sports club that counts. Self-regulated sports exercises (running, cycling, swimming etc) are mostly less regular, and seem to be steered more by good intentions and impulses. These exercises are individual, not socially embedded and without controlling the limits. It might be that stimulation of sports, e.g. by health promotion by authorities,[41,42] motivate some youngsters, in particularly those, who are less involved in peer groups, to do solo exercises. In that respect these youngsters differ from PUF patients, who are members of sports clubs. Participation in groups strengthens self-esteem and development of social skills besides boosting the physical condition,[43] while self-regulated sports exercises, especially when they are not performed regularly, easily carry the risk of a lack of balance between intensity, proportion and recuperation and have not such positive boosting effects, but may lead instead to overloading.[44]

The finding, that the social structure of playing sports is the most likely discriminating factor for the effects of physical exercises, may explain the contradictory results in literature.[36,37] In the Netherlands, sports clubs are not related to schools, and physical education in school is limited to no more than 2 hours weekly, and is easily to evade by those who are not fond of sports. There is no doubt that sports exercises contribute to an active lifestyle with positive effects on health outcome.[42] In promoting youngsters to adopt an active lifestyle, the importance of the socially embedded activities should be stressed.

School and fatigue

Our data in chapter 2 showed that preceding their fatigue the patients had no important self-reported problems with their study in school. Their results were above average and they did not need more time for home work. This means that they did not have to push themselves to the limit. But even for good students some weeks absence from school will turn out in delays that are not easily to catch up without extra help from the teachers and/or classmates. Most of the patients reported to have good relationships with their teachers and most of the patients were growing up in well educated families. It is our clinical experience that most schools offer these patients material assistance, which varies from special classes suited to their abilities to organizing a bed in a special room somewhere in the school for rest between the classes. When the fatigue is persistent for months and there is no prospect of improvement, the usefulness of the extra special assistance will be questioned and the animation for it will decrease. Chapter 6 described the negative effects on school attendance and motivation of the connotation that patient's fatigue complaints correspond with the fatigue of CFS. The use of medical labelling can induce bias in perception,[45,46] and carries the risk of the fatigue becoming self- validating and self-reinforcing,[47,48] and offers a sanctioned pathway for CFS illness behaviour in school.[49] In spite of all good intentions of schools with their special assistance to prevent educational delays, the benefits can be small. The good intentions may even contribute to the persistence of the complaints. So at a certain moment, when the fatigue is going on, a dilemma will arise. When this dilemma is not resolved by the school, and the patient is still under the compulsory education law, the school attendance officer has to be involved. However, in that stage and in that particular school setting it is mostly too late to expect any favourable outcome for the patient. Though it is not clear what the best practice is, good communications between paediatrician, therapists and school from the very beginning might avoid the dead alley. Besides therapies by psychologists and physiotherapists, the management of young PUF patients has in the first place to be geared to the natural environment of the patient, i.e. school and home.

Therapy of patients with Prolonged Unexplained Fatigue in Paediatrics

Cognitive Behavioural Therapy (CBT) has been proved to be effective in a substantial number of young patients with CFS,[50,51] but not in all. CBT for CFS is based on the model of perpetuating factors, and aims at a change in fatigue related cognitions and gradual increase of activity.[52] As far as we know, there is no proved effective therapy for young PUF patients. To introduce CBT for these patients in daily paediatric practice is not easy, even when it should be clearly necessary. Proposals of psychological interventions often encounter resistance in the families of fatigued patients,[53] (and on top of that, when patient and parents accept psychological involvement, it is not always easy to involve actively in the short run a psychologist, who is specialized in CBT.) In the knowledge that the longer fatigue exists, the worse the prognosis will be,[54] we developed an intervention that had to be useable for the paediatric practice. This intervention consisted of a modelling video film, as described in chapter 6, in addition to the treatment as usual by the own paediatrician. However, this intervention had not any effect on the outcome of fatigue severity, but turned out to be associated with less school attendance and less motivation. We supposed that the use of medical labeling in the film might have resulted in patient's perceiving the condition as a disease and this might have contributed to the reinforcement of symptoms and legitimization of functional disabilities. That might have paved the way to CFS illness behaviour, in stead of taking over strategies to cope as presented in the film. We concluded that the label of CFS confirmed the patient and his parents in their beliefs of a somatic disease, which had a negative impact. Though we understand the last guidelines of the Royal College of Paediatrics and Child Health[55] to apply a shorter time criterion for CFS in daily paediatric practice, and though we agree with the focus on the prevention of harm of the educational development, we warn against using the diagnosis “CFS” in these young fatigued patients.

There is no need to know the exact cause of the fatigue to start the management of the fatigue, like there is before treating a broken leg no need to know that the patient was standing on a wobbly stepladder. However, the daily practice is not easy. In the beginning, after the referral to the paediatricians, the patients but foremost the parents are mainly focused on a somatic cause. Furthermore, the vehement opposition by some lay societies against any form of psychological involvement does not facilitate the trust in regular medicine.

The management of ongoing unexplained somatic complaints in general and of fatigue complaints in particular ask for recognition of the seriousness of the complaints.[9] When the paediatrician is capable of establishing a good relationship with patient and parents, based upon mutual trust, and of consistently supporting them by education and encouragement, he can play a leading role in the process of recovery.

Recommendations for clinical practice

The results and limitations of our study, in combination with the work of others lead to several suggestions for guidelines for the management of PUF patients in paediatrics.

Guidelines for management of PUF patients in Paediatrics

- *Keep the period of diagnostic examinations as short as possible to conclude with the high probability that there is no relevant pathology.*
- *Acknowledge the reality of the complaints, but bear in mind the possibility of Paediatric falsification*
- *Use the neutral diagnosis 'Prolonged Unexplained Fatigue (PUF)' or in Dutch 'Aanhoudende Onverklaarde Moeheid (AOM)'*
- *Start the management with a trustworthy explanation of the mechanisms of fatigue.*
- *Consider the prognostic risk and protective factors in the choice of 'subgroup-tailored' therapy. (Cognitive Behaviour Therapy and Graded Exercise Therapy are not panacea's for all patients)*
- *Guide the basic treatment to avoid school absenteeism and to keep in touch with peers and social events.*
- *Guide sleep hygiene to maintain normal times of sleep instead of sleeping into morning hours, and not to lapse into the habit of day time naps.*
- *Organize a team with a psychologist, school doctor and involve the parents in the treatment program by mutual agreements with school and home.*

Opmerking [H.W.2]: Dit mer griit raster o.i.d. weergeven

Recommendations for promotion of Physical Activity and Health

Complete promotion of sports as part of a healthy lifestyle with the addition to practise sports in groups like physical education classes and sports clubs: the social embedding of physical exercises has more better effects on physical strength by the regularity of the exercises and it contributes to the development of social skills.

Suggestions for future research

1. *Distinction of sub-groups with Prolonged Unexplained Fatigue*

The results of our studies support the statement that uniformity among fatigued patients does not exist. Therefore, future research should focus on recognizing patient characteristics in relation to the course of fatigue.

2. *Effects of tailored treatment based on type of subgroups.*

Different subgroups may profit from different therapies.

For example: Graded Exercise Therapy for patients with fear for physical activity, or a relative passive lifestyle; Cognitive Behaviour Therapy for patients with fatigued family members on an individual or on a family basis; clinical instead of outpatient treatment for extremely debilitated patients.

3. Effects of an overall multidisciplinary management of fatigued patients with serious school absence (paediatrician, therapists, school and parents.)

Intervention studies could investigate the obstacles, costs and effectiveness of therapy tuned towards the actual possibilities of the daily environment.

4. Effects of one hour later start of school on fatigue complaints

Adolescents, fatigued as well non fatigued, in the western world are sleeping less hours than they need for optimal rest. Shortage of sleep is a major factor for underperforming in schools and for ongoing fatigue and may be a provoking factor for the development of PUF in vulnerable adolescents.

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Chapter 9

Summary of results

Samenvatting in het Nederlands

Gearfetting Yn it Frysk

Summary

Fatigue is a common complaint in children and adolescents. Ongoing fatigue is less common, but not rare. It brings on health concerns in patients and / or parents, and may be a reason for consulting the general practitioner. When the GP does not find a plausible explanation for the fatigue, and patient and/or parents remain worried, referral to paediatrics may follow. The last years, paediatricians are regularly confronted with these fatigued patients. After excluding somatic and mental diseases there will remain uncertainty about the origins and the prognosis of the complaints. For patient and physician alike, it is difficult to find a way to deal with this. Prolonged unexplained fatigue is the most frequent cause of (partly) school absence and a risk for the social and educational development of youngsters. Most of the patients, who visit the paediatrician for the first time, do not fulfil the criteria for the diagnosis Chronic Fatigue Syndrome, but are not less severe fatigued. Because of the serious limitations and the many uncertainties concerning this illness, the clinician needs more tools to help these young patients.

This thesis is focused on fatigue of such an intensity and duration that the child or adolescent has sought medical help in general paediatrics. The fatigue is not the result of ongoing bodily or mental exertion and can not be explained by any known somatic or mental disease.

In **chapter 1** the use of different definitions of ongoing fatigue in the literature has been discussed. We objected against the adjective “chronic”, because of the negative connotations like “never ending.” Therefore we used in our research the neutral phrase: **Prolonged Unexplained Fatigue (PUF).** Not only in former times but also nowadays, there is tendency to speak about a “fashion phenomenon”, as if is the complaints are not real. It seems that the incidence of disabling fatigue goes up and down in time and by that gives the impression of a fashion. However, the symptoms are still real. The “lump” hypothesis might be an explanation for the fluctuations in incidence. This hypothesis implies that there is a common basis for different medically unexplained conditions, that the expression in

symptoms may be steered by known examples, and that the diagnosis that patients receive is somewhat arbitrary and depends on the focus in health care and society.
In the section pathophysiology of fatigue, we supported the hypothesis that the basis for PUF might be the disturbed homeostasis within the psycho-neuro-immuno-endocrine network, that does not return to rest, and that biological, psychological and social factors are involved.
The view that the disturbance of the homeostasis is continuing, while the cause of the disturbance has been gone, and that some perpetuating factors such as the misinterpretations of bodily signs, wrong sleeping habits and helplessness may obstruct recovery, offers the physician a basis for treatment.

In **chapter 2** the characteristics of the patients are presented. The opinion that epidemic proportions of ongoing fatigue in children and adolescents are related to today's overloaded life style, late bed times and unhealthy habits is not supported by this study. They were educated at mean higher school levels and had serious school absence. Preceding the onset of fatigue they had relatively good school results, did not experience school work as overburdening, and had a life style with less physical (sports and additional jobs) and more sedentary (audiovisual, computer) activities. Although they reported to have a lot of good friends, they had little joint activities with them and went out very rarely. They were growing up in mean higher educated families with considerable more fatigued members and more frequently with separated parents. They had no health condition undermining eating habits nor substance use. They estimated the quality of relations with meaningful persons as good, but patients in one parent families generally qualified the relations with their parents as worse. Most patients had one ore more life events in the year preceding the fatigue complaints.
In comparison with the peer population they did not overburden themselves. Girls were overrepresented like in all studies on fatigue..

In **chapter 3** the results of the 12 months follow up are presented. Half of the patients were still severe fatigued and almost half of them missed school classes for more than 50 %. It turned out that it is possible, already in the early stage of the fatigue, to identify (to some degree) patients with a good or worse development. We found that prior physically inactive lifestyle, sleep problems at initial assessment and some specific somatic symptoms, such as blurred vision and hot and cold spells, predicted the development of persistent fatigue with significant school absence. A moderately active lifestyle preceding fatigue was associated with ahigher probability of a good outcome.

These findings may be important for the prevention and the management of the fatigue.

In **chapter 4** we show the effects of the different types of physical activities on the development of fatigue. We identified already in chapter 3, that previous physical inactivity predicted for a negative, and physical activity for a positive outcome. Regularly cycling between home and school and membership of sports clubs (football, hockey, rowing etc) preceding fatigue, strongly improved the prognosis of fatigue in contrast to self-regulated exercises (running, swimming, cycling etc). The weekly spent time on physical exercises was of less influence than exercising with peers as such.
These findings may be important for advising sports.

In **chapter 5** we describe the sleep habits and sleep problems in non-fatigued and fatigued healthy adolescents and patients with PUF. Sleep shortage was very common in all adolescents. Fatigued controls, by contrast to patients, attributed their fatigue to the combination of going too late to bed and the early school times. They tried to compensate shortage of sleep in weekends, and had more irregularity in their sleep habits. Remarkable was, that fatigued controls also experienced a less sleep quality. Patients attributed their fatigue to illness. They had no irregularity in their sleep habits, estimated their need of sleep above the average for their age, and slept actually more hours. The sleep problems of the patients with PUF, and to a lesser degree of the ‘normal’ fatigued controls were the same as reported in the CFS literature. These findings pointed in the direction of a continuum of sleep problems in adolescents from not fatigued (no problems), via fatigued controls (light problems) to fatigued patients (severe problems). This continuum of sleep problems did not correlate with the sleep quantity. There was a clear distinction between controls and patients. Controls slept significantly shorter and patients longer than the average for their age. We supposed that the sleep/wake brain as pivot for the circadian rhythm of the homeostasis of the bodily functions, acts like an transmitting station with an antenna for the sleep habits and a sender for sleep problems.
This supposition may be the basis for advising sleep hygiene.

In **chapter 6** we describe a randomized controlled trial with a modelling video film. The patients received the film to watch at home alone and with family and friends. The hypothesis was that explaining fatigue symptoms as precursors of Chronic Fatigue Syndrome and showing strategies to cope with the debilitating effects in a video film, might be a good instrument for the general paediatrician to prevent an unfavourable outcome. However, in the follow up one year later the patients, who received the film on top of the usual care, reported the same fatigue severity, more school absence, and less motivation than those who received usual care only. We supposed that these adverse effects were caused by the double message of the video film. Patients particularly picked up the first message, (i.e. fatigue complaints may be the result of a well-known condition: Chronic Fatigue Syndrome) as an explanation and legitimization of their fatigue complaints. The second message (i.e. how to cope successfully with debilitating fatigue and unhelpful thoughts), did not get across. We concluded that labelling CFS on PUF patients may smoothen the way to CFS and has to be avoided.

In **chapter 7** we describe the symptomatic and educational long-term outcome, healthcare use, and risk factors in adolescents with CFS, diagnosed in accordance to the CDC criteria and referred to specialized CFS centre in a tertiary academic paediatric hospital. Without appropriately directed interventions the outcome was disappointing and less optimistic than reported in the literature. Patients used a considerable amount of health care. Older age was a risk factor for an unfavourable outcome. After 3.2 years, about half of the patients were still severely fatigued with serious school absenteeism, impaired physical functioning and bodily pain.

We conclude that, concerning the risk of a serious disturbance of the educational and social development with persistent consequences for the rest of their life, CFS in youngsters is a very serious illness, and trying to prevent this very unfavourable development, patients need appropriate interventions. Only Cognitive Behaviour Therapy with Grade Exercise Therapy has been proved to be effective treatments, but not in all patients, and a reluctance about the psychological approach in CFS patients and their parents is not rare.

It belongs to the professional responsibilities of paediatricians to cope with this reluctance.

The general discussion in **chapter 8** mainly concerns the consequences of our findings for the daily practice of the general paediatrician, who is confronted with a child or adolescent with complaints of ongoing severe fatigue. The general management must be based on confidence, clearness and respect. Distinction between subgroups of patients offers possibilities for more tailored therapies. Initiatives for guidelines and future studies are presented.

Samenvatting

Ieder mens kent in het eigen dagelijks bestaan het gevoel van moeheid of vermoeidheid. Beide woorden worden door elkaar heen gebruikt. Terwijl vermoeidheid meer een gevolg lijkt te zijn van het ‘voorafgaande’, drukt moeheid meer het gevoel van het ‘nu met het oog op straks’ uit. Iemand is ‘vermoeid van’ of ‘te moe om.’ Vermoeidheid kan een positief gevoel zijn en gekoppeld aan tevredenheid, bijvoorbeeld na het volbrengen van een grote inspanning, maar het kan ook een negatief gevoel zijn, als het sneller optreedt dan verwacht of niet over gaat. Moeheid is daarentegen nooit een positief gevoel, maar gekoppeld aan de gedachte om een inspanning te moeten leveren, terwijl ingeschat wordt dat de energie daarvoor te kort zal gaan schieten. Daarnaast kan moeheid ook een uiting van lusteloosheid zijn of zoals in het Duits een tekort aan ‘Antrieb’. Vermoeidheid en moeheid lijken beide een beschermende functie te hebben tegen overbelasting. Vermoeidheid is het waarschuwingssignaal dat het tijd is om te rusten en moeheid meer het preventiesignaal om niet ergens aan te beginnen. Moeheid ontneemt de lust tot zowel fysieke als mentale activiteit, maar betekent niet altijd dat het noodzakelijk is om zich tegen zo een activiteit te beschermen. Fysieke en mentale moeheid kunnen als hetzelfde signaal ervaren worden en verwarrend zijn. Als iemand na langdurige denkwerk vermoeid is en zich te moe voelt om nog wat te gaan doen, maar niet aan deze moeheid toegeeft en bijvoorbeeld toch gaat sporten, is hij na afloop vaak niet uitgeput, maar juist verkwikt. Lichamelijke vermoeidheid is te objectiveren met bijvoorbeeld hartslagmeters en bepalingen van lactaat in het bloed. Moeheid echter kan alleen met behulp van vragenlijsten gemeten worden.

Tijdens het uitvoeren van lichamelijke en mentale inspanningen wordt in de sensorische cortex van de hersenen de ‘sense of effort’ geregistreerd. Dat is de moeite die het kost om met de inspanning door te gaan. De ‘sense of effort’ kan zo groot worden dat de drang om met de inspanning te stoppen groot wordt. In de sportwereld wordt dit het moment van de ‘de man met de hamer’ genoemd. Het principe van training is om tijdelijk voorbij dit waarschuwingssignaal de inspanning vol te houden. Voldoende rust daarna is nodig om de conditie te verbeteren. Bij mentale inspanningen wordt de ‘sense of effort’ waargenomen als de moeite die het kost om de concentratie vast te houden en iets uit het geheugen op te halen. Naast de vermoeidheid en moeheid van alledag, gaan veel ziekten gepaard met moeheid en versneld vermoeid raken. Boodschapper-eiwitten die bij ziekten vrijkomen, zoals cytokines lijken het brein te melden dat de kwetsbaarheid verhoogd is en dat rust genomen moet worden op een veilige plaats, zoals bijvoorbeeld in bed. Dezelfde eiwitten spelen ook een rol bij de

informatieoverdracht van de gevolgen van inspanning vanuit het bewegingsapparaat naar de hersenen.

Dit proefschrift gaat niet over de alledaagse moeheid of de moeheid en versnelde vermoeidheid die bij ziekte voorkomen. Het gaat over de moeheid die het dagelijks leven belemmert en zolang blijft aanhouden dat na verloop van tijd medische hulp gezocht wordt, maar waarbij de arts geen medische oorzaak kan vaststellen.

Moeheid kan in zeer verschillende gradaties voorkomen.: van geheel niet tot extreem moe (het zogenaamd moeheidscontinuüm). Aan de hand van vragenlijsten, zoals de Checklist Individual Strength (CIS-20), kan de ernst van de moeheid uitgedrukt worden in een subjectieve score. De CIS-20 bevat 4 onderdelen en bestaat uit totaal 20 vragen over subjectieve moeheid, motivatie, activiteit en concentratie. Wanneer iemand gedurende tenminste 6 maanden meer dan 40 op een schaal van 8 tot 56 punten op het onderdeel subjectieve moeheid van de vragenlijst scoort en daarnaast tenminste 4 van de 8 bijkomende symptomen heeft, mag de diagnose Chronisch Vermoeidheid Syndroom (CVS) gesteld worden. Deze bijkomende 8 symptomen zijn: niet-verkwikkende slaap, malaise na inspanning, pijnlijke gewrichten, hoofdpijn, spierpijn, keelpijn, gevoelige lymfeklieren in hals en/of oksels en verminderde concentratie en geheugen. Deze voorwaarden voor de diagnose CVS zijn opgesteld om wetenschappelijk onderzoek binnen een nauw omschreven patiëntengroep mogelijk te maken, maar ze blijken voor de dagelijkse medische praktijk vaak niet meer te betekenen dan een nadere aanduiding van de ernst van de klachten. De meeste patiënten met moeheidsklachten die de algemeen kinderarts ziet, voldoen namelijk (nog) niet aan de criteria voor CVS, maar ze zijn wel ernstig moe, beperkt in hun mogelijkheden en vragen om hulp. Wij spreken in dit proefschrift van Aanhoudende Onverklaarde Moeheidsklachten (AOM), vertaald in het Engels als Prolonged Unexplained Fatigue (PUF).

AOM is de meest voorkomende reden voor langdurig geheel of gedeeltelijk schoolverzuim en vormt daardoor een ernstig risico voor de educatieve ontwikkeling van kinderen met soms blijvende gevolgen voor latere arbeidsmogelijkheden. Bovendien kan hun sociale ontwikkeling door het missen van gezamenlijke activiteiten met leeftijdsgenoten beperkt worden. AOM is voor kinderen en adolescenten dan ook een serieus probleem. Over het voorkomen van AOM in Nederland zijn geen goede betrouwbare getallen bekend, maar iedere algemeen kinderarts wordt enkele malen per jaar met een patiënt geconfronteerd die met deze klachten door de huisarts verwezen is. Wel is bekend dat in Nederland jaarlijks 1% van alle jongeren de huisarts bezoekt vanwege moeheid. De meesten herstellen binnen een maand, maar 0.02 % voldoet aan de criteria voor CVS. Ook is bekend dat veel jongeren klagen over moeheid zonder naar de dokter te gaan. In een groot steekproefonderzoek onder middelbare scholieren in Utrecht meldden ruim 13% ernstige moeheid, en dat kwam 3 keer zoveel voor bij meisjes als bij jongens. Ruim een kwart van hen had een jaar later nog dezelfde moeheidsklachten. Veel vermoeide jongeren zullen moeheid als een feitelijk gegeven van hun dagelijks leven beschouwen, maar enkelen zijn door de aard van moeheid bezorgd over hun gezondheid en gaan om die reden naar de huisarts. Als deze geen oorzaak vindt en de patiënt daarmee niet gerustgesteld is, kan een verwijzing naar de kinderarts volgen. Over deze kinderen en adolescenten gaat dit proefschrift. Zij vormen een groep aan het eind van het moeheidsspectrum, maar zij voldoen (nog) niet aan de CVS- voorwaarden. Ze worden ernstig beperkt in hun mogelijkheden, zijn ongerust over hun gezondheid en zoeken medische hulp ‘hogerop’. Hiermee is echter niet gezegd, dat zij ernstiger moe zijn dan leeftijdsgenoten die niet bij de kinderarts komen. In ieder geval hebben zij andere attributies voor hun moeheid. Kinderartsen vinden het doorgaans ‘moeilijke patiënten’, omdat enerzijds een onderliggende ziekte nooit voor 100% is uit te sluiten en anderzijds voortdurend aanvullend onderzoek het herstelproces belemmert of zelfs de klachten kan doen toenemen. Bovendien is het niet duidelijk wat de beste behandeling is, omdat deze patiënten geen homogene groep vormen. De behandeling die voor de ene patiënt tot een gunstige ontwikkeling leidt, hoeft bij een andere patiënt niet hetzelfde effect te hebben en zou zelfs tot een verslechtering kunnen leiden.

Geconfronteerd met deze, voor zowel de kinderarts als de patiënt frustrerende situatie, hebben wij van uit de algemene kinderartsenpraktijk onderzoek gedaan naar jonge patiënten met moeheidsklachten. Verspreid over het gehele land namen een dertigtal kinderartsen met een positieve attitude ten aanzien van AOM deel aan dit onderzoek. We zochten antwoord op vragen als: wat zijn het voor kinderen en adolescenten die maar moe blijven, hoe is het beloop van hun klachten en is er een praktische mogelijkheid voor de kinderarts om het beloop gunstig te beïnvloeden. We deden onderzoek naar kenmerken zoals familieachtergrond, schooltype, inspanningen voor schoolwerk, schoolresultaten, vrijetijdsbesteding, levensgebeurtenissen, eet- en slaapgedrag, alcohol-, tabaks- en drugsgebruik. Daarnaast zochten we naar mogelijke factoren die de ontwikkeling van de moeheid zouden kunnen voorspellen en naar het meerjarenverloop van de moeheid bij patiënten die uiteindelijk aan de criteria voor de diagnose CFS voldeden.

In de algemene inleiding van dit proefschrift stellen we dat het bijvoeglijk naamwoord *chronisch* in relatie tot vermoeidheid ongelukkig is, omdat daarmee gesuggereerd wordt dat de vermoeidheid blijvend zal zijn, terwijl de inzet van behandeling juist op herstel gericht is. Om het onverklaard zijn van de moeheid toch te kunnen begrijpen, wordt uitgegaan van de hypothese van de homeostasis. Dat is het dynamische evenwicht tussen de verschillende op elkaar afgestemde systemen van lichaam en geest, het zogenaamde psycho-neuro-immuno-endocriene netwerk. Dit evenwicht kent naast het dag/nachtritme, maandelijkse en zomer/winterritmes. Via ieder afzonderlijke systeem kan het evenwicht door geheel verschillende factoren verstoord raken. Deze factoren worden ‘uitlokkende factoren’ genoemd. De veronderstelling is, dat een verstoord evenwicht gepaard gaat met een verminderd vermogen voor activiteit en dat dit verminderd vermogen gevoeld wordt als moeheid en versneld optredende vermoeidheid. Normaal herstelt het evenwicht zich en verdwijnt de moeheid als de oorzaak van de verstoring niet meer aanwezig is. Maar soms zijn er andere factoren die, ook al is de oorzaak al verdwenen, toch het herstel van het evenwicht belemmeren. Deze factoren worden ‘onderhoudende factoren’ genoemd. De behandeling van aanhoudende klachten waarvan de oorzaak niet meer aanwezig, moet zich dan ook richten op deze onderhoudende factoren.

In hoofdstuk 2 wordt de mening dat veel jongeren moe zijn als het gevolg van een overladen leefstijl, voor deze specifieke patiëntengroep weerlegd. De patiënten hadden geen ongezonde eetgewoonten en gebruikten geen alcohol, tabak of drugs. Ze hadden in de aan de moeheid voorafgaande periode minder lichamelijk inspannende vrijetijdsactiviteiten, maar daarentegen meer creatieve en culturele activiteiten zonder dat deze buitensporig waren. Ook keken ze meer televisie, wat kan duiden op een verhoogde neiging tot zittende ontspanning of een gebrek aan mogelijkheden of stimulatie om hun vrije tijd actiever te besteden. Ze hadden naar eigen inschatting goede verhoudingen met hun leeftijdsgenoten, maar weinig gezamenlijke activiteiten. De patiënten volgden een gemiddeld hoger schooltype, net als hun ouders indertijd, maar zij voelden zich niet overbelast met schoolwerk.

In de gezinnen zijn vaker meer leden met dezelfde moeheidsklachten. Dit zou op erfelijke factoren kunnen duiden, maar evenzeer op gezinsdynamiek. Meisjes zijn oververtegenwoordigd. De patiënten zijn niet alleen ernstig moe, maar hebben daarnaast ook meerdere andere lichamelijke klachten. De kenmerken van de patiënten zijn wel onderscheidend van gezonde leeftijdsgenoten, maar niet van patiënten met CVS. Dit betekent dat het onderscheid tussen patiënten met CVS en AOM een kunstmatige en voor de klinisch praktijk niet noodzakelijke is.

In hoofdstuk 3 wordt beschreven dat 50% van de patiënten na 12 maanden nog niet hersteld is. Reeds bij het eerste bezoek aan de kinderarts werden enkele factoren gevonden die voorspellend waren voor het beloop van de moeheid. Naast slaapproblemen en ernst van moeheid in het begin, waren enkele bijkomende klachten voorspellend voor een ongunstige ontwikkeling: koude rillingen, wazig zien, pijn in ledematen en rug, obstipatie en geheugenproblemen. Daarentegen voorspelden het mannelijke geslacht en een actieve levensstijl voorafgaande aan de moeheid juist een gunstig verloop. Op basis van deze verschillende voorspellende factoren zou in plaats van een eenheidsbehandeling een meer op de individuele patiënt gerichte behandeling vorm gegeven kunnen worden.

In hoofdstuk 4 wordt duidelijk dat het sociale aspect en de begrenzing van trainingsprogramma's bepalen of een leefstijl met sportbeoefening een beschermende factor tegen persisterende moeheid is of niet. Het blijkt dat lidmaatschap van een sportclub wel beschermt en sporten op eigen houtje juist niet. Dit verschil kan uitgelegd worden door de regelmaat van de sportbeoefening onder leiding van een trainer en het samen sporten met leeftijdsgenoten. Binnen een sportclub is de sociale interactie vaak groot en de kans op overbelasting gering, tenminste als niet topsport wordt nagestreefd. Zelfgeorganiseerde sportbeoefening is vaak een meer impulsief gevolg van het besef dat sporten goed voor de gezondheid zou zijn, met het risico van overdrijving. Het lid zijn van een sportclub is voor veel jongeren bijna een vanzelfsprekendheid en het stimuleren daarvan door ouders vaak een onderdeel van de opvoeding. Jongeren die buiten een club om sporten zijn daardoor mogelijk al verschillend. Propaganda om meer te sporten vanwege het gunstige effect dat lichamelijke activiteit op de gezondheid zou hebben, kan voor deze kinderen een verkeerde uitwerking hebben.

In hoofdstuk 5 worden de duur, regelmaat en kwaliteit van slaap van de patiëntengroep vergeleken met een groep van gezonde leeftijdsgenoten die ook klagen over moeheid en met een groep van gezonde leeftijdsgenoten zonder klachten. Alle jongeren in het onderzoek gaven aan slaaptekort te hebben. De vermoeide maar gezonde jongeren hadden het meeste slaaptekort, maar ook de meeste onregelmatigheid tussen school- en weekeinddagen. Opvallend is dat meer slaaptekort en meer onregelmatigheid gepaard gingen met meer slaapproblemen en minder slaapkwaliteit.

De patiënten hadden een slaapduur die aanzienlijk langer was dan voor hun leeftijd te doen gebruikelijk of nodig geacht wordt. Toch meldden ook zij nog een slaaptekort. Zij hadden bovendien de meeste slaapproblemen en de minste slaapkwaliteit. Het lijkt dat er naast het continuüm van moeheid een continuüm van slaapkwaliteit bestaat. Hoe meer moe, hoe meer slaap- problemen en hoe minder slaapkwaliteit. We veronderstellen dat moeheid en verminderde slaapkwaliteit beide symptomen zijn van een gezamenlijk onderliggende stoornis. De in hoofdstuk 1 beschreven homeostasis van de verschillende regelsystemen van lichaam en geest wordt beïnvloed door het circadiaan (24-uurs) ritme. Tijdens de puberteit verandert het kinderlijke circadiaanritme in de volwassen vorm. Daarnaast ontstaat een grotere weerstand tegen slaperigheid en kunnen adolescenten het naar bed gaan langer uitstellen, terwijl de slaapbehoefte niet af-, maar zelfs toeneemt. Verondersteld wordt dat door slaaptekort en onregelmatig slaapgedrag de overgang naar een volwassen circadiaanritme verstoord kan raken, waardoor slaapproblemen kunnen ontstaan. En andersom, dat het circadiaanritme wordt verstoord door een in eerste instantie verstoorde homeostasis. Het verstoorde 24-uursritme veroorzaakt vervolgens slaapproblemen. .

Wij adviseren om de overgang naar een volwassen circadiaanritme ongestoord te laten verlopen door zich in de adolescentie zoveel mogelijk aan de fysiologische slaapbehoefte en regelmaat te houden. Omdat een dergelijk advies voor gezonde adolescenten in de hedendaagse wereld onmogelijk is op te volgen, zouden ter preventie van slaaptekort bij adolescenten de middelbare scholen ‘s morgens een uur later moeten beginnen. Een gunstige uitwerking op de leerresultaten is in verschillende onderzoeken al eerder vastgesteld.

In hoofdstuk 6 wordt een onderzoek beschreven waarbij patiënten, die naast de gebruikelijke kindergeneeskundige behandeling, door het lot bepaald een videofilm ontvingen, worden vergeleken met patiënten die alleen de gebruikelijke behandeling kregen. De videofilm toonde de effecten van aanhoudende moeheid op het dagelijks leven van een aantal patiënten met CVS en hun strategieën om daar zo goed mogelijk mee om te gaan. De verwachting was dat dit een goed bruikbaar instrument voor de kinderarts zou kunnen zijn om aan de gangbare behandeling van patiënten met AOM toe te voegen. Het effect van de videofilm was echter dat de patiënten die de film ontvingen om thuis met familie en vrienden te bekijken een jaar later niet minder ernstig moe waren, maar wel meer schoolverzuim hadden en minder gemotiveerd waren op de CIS-20 motivatie subscore, dan de patiënten die de film niet hadden gekregen. Dit onverwachte effect wordt toegeschreven aan de dubbele boodschap van de film. De patiënten pikten wel de uitleg en erkenning van de moeheidsklachten op, maar niet de boodschap hoe hier goed mee om te gaan. Het gebruik van medische termen kan er toe bijdragen dat klachten door patiënten meer als een ziekte worden ervaren, waardoor symptomen worden benadrukt en ziektegedrag meer wordt gelegitimeerd. De lering die we uit dit onderzoek hebben getrokken is, dat een bestempeling van moeheidsklachten, als CVS klachten weliswaar meer duidelijkheid kan verschaffen aan patiënten die niet aan de CDC criteria voor CVS voldoen, maar niet doelmatig is en zelfs contraproductief met betrekking tot herstel. Zonder aan de erkenning van de klachten te tornen, moet het gelijkschakelen van AOM-klachten aan CVS-klachten voorkomen worden.

In hoofdstuk 7 wordt het verloop van moeheid bij adolescenten met CVS beschreven. Het in de literatuur beschreven gunstige beloop van de moeheid bij jongeren met CVS kon niet bevestigd worden. De patiënten maakten aanvankelijk zeer frequent gebruik van de gezondheidszorg, terwijl de gezondheidszorg weinig adequate hulp had te bieden. Meer dan 50 % van de patiënten met CVS was na ruim 3 jaar nog even vermoeid met dezelfde verdere symptomen en ernstig schoolverzuim. Terwijl de adolescentie bij uitstek de periode in een mensenleven is waarin geëxperimenteerd moet kunnen worden om in een ruimere wereld dan die van thuis een plaats te vinden, staat deze periode bij deze patiënten in het teken van aanhoudende moeheid met veel beperkingen. Deze studie onderstreept de ernst en impact van aanhoudende moeheidsklachten zonder medische of psychologische verklaring op de jonge leeftijd en laat geen plaats over voor een negatieve attitude ten aanzien van deze klachten.

In de algemene discussie worden de consequenties van de uitkomsten van deze studie in verhouding tot de literatuur besproken en voorstellen gedaan voor de praktijk van de kinderarts. Het onderzoek naar onderliggende pathologie voor de moeheidsklachten kan beperkt zijn en moet zo snel als mogelijk is afgerond worden om onzekerheid niet te laten voortduren. De erkenning van de realiteit van de klachten, empathie voor de patiënt en een begrijpelijke en duidelijke uitleg vormen de basis van iedere medische behandeling, maar juist bij deze patiënten vormt de duidelijke uitleg een cruciaal probleem. De diagnose Aanhoudende Onverklaarde Moeheid verhoudt zich immers per definitie moeilijk met voldoende duidelijkheid. Een voorbeeld van een metafoor met uitlokkende en onderhoudende factoren kan de patiënt en ouders meer inzicht geven in het mechanisme dat eraan ten grondslag ligt. Het moet de patiënt duidelijk zijn dat lichaam en geest in dezen een onlosmakelijk eenheid vormen. Het herkennen van voorspellende factoren kan veel betekenis hebben voor de behandeling specifiek afgestemd op de betreffende patiënt. Het primaire doel van de behandeling is, dat de patiënt zich niet isoleert, maar zo veel mogelijk aan school en sociale activiteiten blijft meedoen. Hierbij is het van belang om onderscheid tussen passieve en relatief actieve patiënten te maken, omdat sommigen aangespoord en anderen juist eerder afgeremd moeten worden. Om goed met de interpretaties en attributies van de klachten om te leren gaan, is cognitieve gedragstherapie (CGT) ook bij jongeren een aangetoonde effectieve vorm van hulp. Deze therapie kan echter alleen kans van slagen hebben als de patiënt geen weerstand tegen een psychologische benadering heeft. Iedere behandeling moet afgestemd zijn op de mogelijkheden van thuis en school. Hiervoor is een structureel multidisciplinair overleg met school en thuis noodzakelijk binnen de ruimtes die het medisch beroepsgeheim en de leerplichtwet bieden.

Gearfetting

Eltsenien hat yn syn deistich bestean weet fan it gefoel fan wurchte of wurgens. Beide wurden wurde troch elkoar hinne brûkt. Wylst wurgens mear in gefolch liket te wêzen fan wat der oan foarôf gie, jout wurchte mear it gefoel wer fan "no mei it each op aansen". Immen is "wurch fan" of "te wurch om" . Wurgens kin in posityf gefoel wêze en keppele oan tefredenheid, bygelyks nei it folbringen fan in grutte ynspanning, mar it kin ek in negatyf gefoel wêze, as it gauwer komt as it ferwachte waard en net oer giet. Wurchte is dêr foaroer noait in posityf gefoel, mar keppele oan de gedachte om in ynspanning te leverjen, wylst wol te foarsjen is dat de energy dêrta te lyts wêze sil. Dêrnjonken kin wurchte ek in utering wêze fan lusteleazens of sa't it yn it Dútsk sein wurdt in tekoart oan "Antrieb". Wurgens en wurchte lykje beide in beskermjende funksje te hawwen tsjin oerbelêsting. Wurgens is it warskôgingssynjaal dat it tiid wurdt om rêst te nimmen en wurchte mear in previnsjesynjaal om earne net oan te begjinnen. Wurchte benimt jin de oanstriid ta sawol fysike as mentale aktiviteit, mar betsjut net altyd dat it needsaaklik is om jin tsjin sa'n aktiviteit te beskermjen.

Fysike en mentale wurgens kinne as itselde synjaal belibbe wurde en betiizjend wêze. As immen nei lang tinkwurk wurch is en him te wurch fielt om noch wat te dwaan, mar net oan dizze wurchte tajout en bygelyks dochs oan it sporten giet, is hy nei ôfrin dêr fan fakentiden net ynein, mar krekt ferkwikt.Lichamelike wurgens is te objektivearjen mei bygelyks hertslachmjitters en it bepalen fan lactaat yn it bloed. Wurchte kin allinne mei help fan fragelisten metten wurde.

Under it útfieren fan lichamelike en mentale ynspannings wurdt yn de sensoryske kortex fan de harsens de "sense of effort" registrearre. Dat is de muoite dy't it ferget om mei de ynspanning troch te gean. De "sense of effort" kin sa grut wurde dat de oantrún om mei de ynspanning op te hâlden te grut wurdt. Yn de sportwrâld wurdt dit it moment fan de "de man mei de hammer" neamd. It prinsipe fan trening is om tydlik nei dit warskôgingssynjaal de ynspanning fol te hâlden. Foldwaande rêst is dêrnei nedich om de kondysje te ferbetterjen. By mentale ynspannings wurdt de " sense of effort" waarnommen as de muoite dy't it ferget om de konsintraasje fêst te hâlden en eat út it ûnthâld omheech te heljen.

Neist de wurgens en wurchte fan al den dei binne der in soad sykten dy't mank gean mei wurchte en te gau wurch wurde. Boadskipper-eiwiten dy't by sykte frijkomme, sa as cytotkines lykje it brein te melden dat de kwetsberens ferhege is en dat rêst nommen wurde moat op in feilich stee, bygelyks op bêd. Deselde eiwiten spylje ek in rol by de ynformaasjeoerdracht fan de gefolgen fan ynspanning út it bewegingsapparaat wei nei de harsens ta.

Dit proefskrift giet net oer de gewoane wurgens of oer de wurgens en it earder wurch wêzen dat by sykten foarkomt. It giet oer de wurchte dy’t it deistich libben yn it paad stiet en sa lang oanhâldt, dat nei ferrin fan tiid medyske help socht wurdt, mar dêr’t de dokter gjin medyske oarsaak fan fêststelle kin.

Wurchte kin yn hiel wat gradaasjes foarkomme: fan hielendal nèt oant ekstreen wurch (it saneamde wurgenskontinuüm) Oan de hân fan fragelisten, sa as de Checklist Individual Strength (Cis-20), kin de earnst fan de wurchte útdrukt wurde yn in subjektive skoare. De Cis-20 befettet 4 ûnderdielen en bestiet út 20 fragen oer subjektive wurchte, motivaasje, aktiviteit en konsintraasje. As immen op syn minst seis moanne lang mear as 40 skoart op in skaal fan 8 oant 56 punten op it ûnderdiel subjektive wurchte fan de fragelist en dêrnjonken 4 fan de 8 bykommende symptomen hat, mei de diagnose Oanhâldend Wurgens Syndroom (Chronic Fatigue Syndrome (CFS)) fêststeld wurde. Dizze bykommende 8 symptomen binne: net-ferkwikkende sliep, aaklik fielen nei ynspanning, pynlike gewrichten, pineholle, spierpine, gefoelige lymfeklieren yn’e hals en/of oksels en fermindere konsintraasje en ûnthâld. Dizze foarwaarden foar de diagnose CFS binne opsteld om wittenskiplik ûndersyk binnen in dúdlik omskreaune groep fan pasjinten mooglik te meitsjen, mar it docht bliken dat se foar de deistige medyske praktyk faak net mear te betsjutten ha as in neiere oantsjutting fan de earnst fan de klachten. De measte pasjinten mei klachten oer wurgens dy’t de algemien-bernedokter sjocht, foldogge nammentlik noch net oan de kritearia foar CFS, mar se binne wol slim wurch, beheind yn harren mooglikheden en se freegje om help. Wy prate yn dit proefskrift oer Oanhâldende Net Ferklearre Klachten oer Wurchte, oerset yn it Ingelsk Prolonged Unexplained Fatigue (PUF)

PUF is de meast foarkommende reden foar skoallefersom dat fan lange duer is of net ophâldt, en sadwaande in earnstich risiko foarmet foar de edukative ûntjouwing fan bern mei bytiden bliuwende gefolgen foar lettere mooglikheden om oan wurk te kommen. Boppedat kin harren sosjale ûntwikkeling troch it missen fan mienskiplike sosjale aktiviteiten mei leeftiidsgenoaten beheind wurde. PUF is foar bern en adolesinten dan ek in earnstich probleem. Oer it tefoaren kommen fan PUF yn Nederlân binne gjin goede betroubere getallen bekend, mar eltse algemien-bernedokter hat in oantal kearen jiers te krijen mei in pasjint dy’t mei dizze klachten troch de húsdokter nei him trochferwiisd is. Wol is bekend dat yn Nederlân jierliks 1 % fan alle jongerein by de húsdokter komt fanwegen wurchte. De measten knappe binnen in moanne op, mar 0.02% foldocht oan de kritearia foar CFS.

Ek is bekend dat in soad jongerein klaget oer wurchte sûnder dat se nei de dokter ta geane. Yn in grut streekproefûndersyk ûnder middelbiere skoalgeande bern makke 13 % melding fan slimme wurchte, en dat kaam 3 kear sa faak foar by famkes as by jonges. In goed jier letter hie in fjirde part fan harren noch deselde klachten. In soad wurge jongerein sil wurchte as in feitlik gegeven fan it deistige libben beskôgje, mar der binne ek dy't har troch de aard fan de wurgens soargen meitsje oer harren sûnens en dy geane om dy reden nei de húsdokter. As dizze gjin oarsaak fynt en de pasjint sadwaande net gerêststeld is, kin in ferwizing nei de bernedokter folgje. Oer dizze bern en adolesinten giet dit proefskrift. Hja foarmje in groep oan de ein fan it wurchtespektrum, mar hja foldogge (noch) net oan de CFS-foarwaarden.. Hjirmei is net sein dat hja slimmer wurch binne as de leeftydsgenoaten dy't net by de bernedokter komme. Yn elts gefal skriuwe hja harren wurchte oan oare oarsaken ta. Bernedokters fine it troch de bank nommen "drege" pasjinten, om't oan de iene kant in ûnderlizzende sykte nea foar 100 % út te sluten is en oan de oare kant hieltyd oanfoljend ûndersyk it proses fan it better wurden yn it paad stiet of sels de klachten tanimmen docht. Boppedat is it net dúdlik wat de bêste behanneling is, om't dizze pasjinten net in homogene groep foarmje. De behanneling dy't foar de iene pasjint in geunstich gefolch hat, hoecht by in oare pasjint net oan te slaan en soe sels negatyf wurkje kinne.

Konfrontearre mei dizze sitewaasje, dy't sawol foar de bernedokter as de pasjint frustrearjend is, hawwe wy út ús algemiene bernedokterpraktyk wei, ûndersyk dien nei jonge pasjinten mei klachten oer wurchte. Ferspraat oer it hiele lân diene namen in tritichtal bernedokters mei in positive attitude wat PUF oanbelanget diel oan dit ûndersyk. Wy sochten om it andert op fragen as: wat binne it foar bern of adolesinten dy't mar wurch bliuwe, hoe is it ferrin fan harren klachten en bestiet der in praktyske mooglikheid om it ferrin geunstich te beynfloedzjen.

Wy diene ûndersyk nei skaaimerken sa as famylje eftergrûn, skoallesoart, ynspanning foar it skoalwurk, skoallerisseltaten, frije-tiids-besteging, wat se yn har libben meimakke hiene, yt- en sliepgedrach, alkohol- tabaks- en drugsgebrûk. Dêrnjonken sochten wy nei mooglike faktoren dy't it ûntstean fan wurgens by pasjinten foarsizze koene en nei in mearjierrenferrin fan wurchte by pasjinten dy't by eintsjebeslút foldiene oan de kritearia foar de diagnose CFS.

Yn de algemiene ynlieding fan dit proefskrift ponearje wy de stelling dat it eigenskipswurd *chronisch* yn relaasje ta wurgens net lokkich keazen is, om't dêrmei suggerearre wurdt dat de wurgens bliuwend wêze sil, wylst de ynset fan de behanneling krekt op better wurden rjochte is. Om it net ferklearre wêzen fan de wurchte dochs begripe te kinnen, wurdt útgien fan de hypothese fan de homeostasis. Dat is it dynamyske lykwicht tusken ferskillende op elkoar ôfstimde systemen fan lichem en geast, it saneamde psycho-neuro-immuno-endocrine netwurk. Dit lykwicht bestiet neist it dei/nacht ritme út moanne - en simmer/winterritmes.

Troch elts systeem apart kin it lykwicht troch folslein ferskillende faktoren fersteurd reitsje. Dizze faktoaren wurde “útlokjende faktoaren neamd” Der wurdt tocht dat in fersteurd lykwicht lyk op giet mei in fermindere fermogen ta aktiviteit en dat dit fermindere fermogen field wurdt as wurchte en gau opkommende wurgens. Normaal komt it lykwicht werom en ferdwynt de wurchte as de oarsaak fan de fersteuring net mear oanwêzich is. Mar soms binne der oare faktoaren dy’t, ek al is de oarsaak ferdwûn, dochs it better wurden fan it lykwicht yn it paad steane. Dizze faktoaren wurde “ûnderhâldende faktoaren” neamd. De behanneling fan oanhâldende klachten dêr’t de oarsaak net mear fan oanwêzich is, moat him dan ek rjochtsje op dizze ûnderhâldende faktoaren.

Yn haadstik 2 wurdt de miening dat in soad jongerein wurch is as gefolch fan in oerladen leefstyl, foar dizze spesifike pasjintengroep werlein. De pasjinten hiene gjin siik meitsjende ytgewoanten en brûkten gjin alkohol, tabak of drugs. Hja hiene yn de tiid foar de wurchte minder lichamelik ynspannende frije tiidsaktiviteiten, mar krekt wol mear kréative en kulturele aktiviteiten sûnder dat dy bûtenspoarich wiene. Ek seagen se mear tillevyzje, wat wize kin op in ferhege oanstriid ta sittende ûntspanning of in gebrek oan mooglikheden of stimulânsen om har frije tiid aktiver te besteegjen. Hja hiene nei eigen ynskatting goede ferhâldings mei harren leeftiidsgenoaten, mar net in soad mienskiplike aktiviteiten. De pasjinten folgen troch de bank in heger skoalletype, krekt as harren âlden eartiids, mar se fielden harren net oerbelêste mei skoalwurk.

Yn de húshâldings binne der faker mear leden mei deselde wurchteklachten. Dit soe op erflike faktoaren wize kinne, mar ek op de dynamyk fan sa’n gesin. Famkes binne talriker fertsjinwurdige as jonges. De pasjinten binne net allinne slim wurch, mar hawwe dêrneist ek meardere oare lichamelike klachten. De skaaimerken fan de pasjinten ûnderskiede har wol fan dy fan oare leeftiidsgenoaten, mar net fan pasjinten mei CFS. Dit bestjut dat it ûnderskied tusken pasjinten mei CFS en PUF in keunstmjittich en foar de klinyske praktyk net needsaaklik is.

Yn haadstik 3 wurdt beskreaun dat 50% fan de pasjinten nei 12 moanne noch net wer better is. Al by de earste besite oan de bernedokter waarden inkelde faktoaren fûn dy’t al in foarsizzing wiene foar it ferrin fan de wurchte. Njonken sliepproblemen en de earnst fan de wurchte yn it begjin, wiene inkelde bykommende klachten foarboaden foar in ûngeunstige ûntjouwing: kâlde rillings, wazich sjen, pine yn ledematen en rêch, ostipaasje en problemen.

mei it ûnthâld. Dêr foar oer stiet dat it feit dat ien fan it manlik geslacht wie, en yn de tiid foar de wurchte tige aktyf, krekt foarboade wiene fan in geunstich ferrin. Op basis fan dizze ferskillende foarsizzende faktoaren soe ynstee fan foar elts de selde behanneling in mear op de yndividuele pasjint rjochte behanneling tapast wurde kinne.

Yn haadstik 4 wurdt dúdlik dat it sosjale aspekt en de begrinzing fan treningprogramma’s útmeitsje of in libbenswize mei sportbeoefening in beskermjende faktor tsjin wurchte is of net. It docht bliken dat it lidmaatskip fan in sportklub wol beskermet en sporten op eigen ban en boet krekt net. Dit ferskil kin útlein wurde troch de regelmaat fan de sportbeoefening ûnder lieding fan in trener en it mei elkoar oan sport dwaan mei leeftiidsgenoaten. Yn in sportklub is de sosjale ynteraksje faak grut en de kâns op tefolle belêsting lyts, benammen as der gjin topsport neistribbe wurdt. Sels organisearre sportbeoefening is fakentiden in mear ympulsyf gefolch fan it besef dat oan sport dwaan goed foar de sûnens wêze soe, mei it risiko fan oerdriuwing. It lidmaatskip fan in sportklub is foar in soad jongerein hast fanselssprekkend en it stimulearjen dêrfan troch de âlden faak in part fan de opfieding. Jongerein dy’t bûten in klub om sport beoefent is dêrtroch mooglik al oars. Propaganda om mear oan sport te dwaan fanwegen it geunstige effekt dat lichamelike aktiviteit op de sûnens hawwe soe, kin foar dizze bern in ferkearde útwurking hawwe.

Yn haadstik 5 wurde de doer, de regelmaat en de kwaliteit fan de sliep fan de pasjintengroep fergelike mei in groep sûne leeftiidsgenoaten dy’t ek kleie oer wurchte en mei in groep sûne leeftiidsgenoaten sûnder klachten. Alle jongeren yn it ûndersyk joegen oan te min sliep te krijen. De wurge mar sûne jongelju hiene it measte tekoart oan sliep, mar dy hiene ek it grutste ferskil tusken de gewoane skoalledagen en de dagen fan it wyk-ein. Opfallend is dat tekoart oan sliep en ûnregelmjittigens lyk op giene mei mear sliepproblemen en minder sliepkwaliteit.

De pasjinten hiene in sliepdoer dy’t aardich langer wie as foar harren leeftiid gebrûklik of nedich achte wurdt. Nettsjinsteande dàt makken ek hja melding fan in tekoart oan sliep. Hja hiene boppedat de measte sliepproblemen en de minste sliepkwaliteit. It liket der op dat der neist it kontinuüm oan wurchte in kontinuüm oan sliepkwaliteit bestiet.

Hoe wurger, hoe mear sliepproblemen en hoe minder sliepkwaliteit. Wy tinke dat wurchte en fermindere sliepkwaliteit beide symptomen binne fan in ûnderlizzende steuring. De yn haadstik 1 beskreaune homeostasis fan de ferskillende regelsystemen fan lichem en geast wurde beynfloede troch it circadiaan (24-oeren) ritme. Yn de puberteit feroaret it berne-circadiaanritme yn de folwoechsen foarm. Dêrnjonken ûntstiet der in gruttere wjerstân tsjin sliepperichheid en kinne adolesinten it op bêd gean langer útstelle, wylst it ferlet fan sliep net ôf- mar sels tanimt. Der wurdt tocht dat troch tekoart oan sliep en ûnregelmjittich sliepgedrach de oergong nei in folwoechsen circadiaanritme fersteurd reitsje kin, dêr't slieppproblemen troch ûntstean kinne. En oarsom, dat it circadiaanritme fersteurd wurdt troch in yn earste ynstânsje fersteurde homeostasis. It fersteurde 24-oersritme is dêrnei mandélich oan slieppproblemen.

Wy riede oan om de oergong nei in folwoechsen circadiaanritme sûnder steurings ferrinne te litten troch yn de adolesinsjetiid safolle mooglik fêst te hâlden oan de fysiologyske behoefte oan sliep en regelmaat. Om't sa'n advys foar sûne jong folwoechsenen yn de wrâld fan hjoed-de-dei ûnmooglik op te folgjen is, soene om it slieptekoart foar te kommen de middelbiere skoallen moarns in oere letter begjinne moatte. In geunstige útwurking op de learresultaten is yn ferskillende ûndersiken al earder fêststeld.

Yn haadstilk 6 wurdt in ûndersyk beskreaun wêrby pasjinten, dy't neist de gebrûklike berne-genêskundige behanneling, in troch lotsjen bepaalde fideofilm krigen, fergelike wurde mei pasjinten dy't allinne mar de gebrûklike berne-genêskundige behanneling krigen.De fideofilm toande de effekten fan oanhâldende wurchte op it deistige libben fan in oantal pasjinten mei CFS en harren strategieën om dêr sa goed mooglik mei om te gean. De ferwachting wie dat dit in goed brûkber ynstrumint foar de bernedokter wêze soe om ta te foegjen oan de gongbere behanneling fan pasjinten mei PUF. It effekt fan de fideofilm wie lykwols dat de pasjinten dy't de film krigen om thús mei famylje en freonen te besjen, in jier letter net minder slim wurch wiene, mar wol mear skoallefersom hiene en minder motivaasje hiene op de CIS-20 motivaasje sub-skoare, as de pasjinten dy't de film net krigen hiene. Dit ûnferwachte effekt fan de film wurdt taskreaun oan it dûbele boadskip fan de film. De pasjinten hellen de útlis en erkenning fan de klachten der wol út, mar net it boadskip om der goed mei om te gean. It brûken fan medyske termen kin der ta bydrage dat klachten troch pasjinten mear as in sykte opfette wurde, wêrtroch symptomen de klam krije en syktegedrach legitimearre wurdt. Wat wy leard hawwe fan dit ûndersyk is, dat in beneaming fan wurchteklachten as CFS klachten oan de iene kant mear dúdlikens jaan kinne oan pasjinten dy't net oan de CDC kritearia foar CFS foldogge, mar net doelmjittich is en sels kontraproduktyf wurket op it herstel. Sûnder oan it erkennen fan de klachten te kommen, moat it lykskeakeljen fan PUF-klachten oan CFS-klachten tefoaren kommen wurde.

Yn haadstik 7 wurdt it ferrin fan wurchte by adolesinten mei CFS beskreaun. It yn de literatuer beskreaune geunstige ferrin by jongerein mei CFS koe net befêstige wurde. De pasjinten makken yn it begjin in soad gebrûk fan de sûnenssoarch, wylst de sûnenssoarch mar in bytsje adekwate help te bieden hie. Mear as 50% fan de pasjinten mei CFS wie nei trije jier noch like wurch mei de selde symptomen en earnstich skoallefersom. Wylst de adolesinsje yn in minskelibben by útstek in tiid is, dat der eksperimenteard wurde moatte kin, om in plak te finen yn in widere wrâld as dy fan thús, stiet dizze tiid by dizze pasjinten yn it teken fan oanhâldende wurchte mei in soad beheinings. Dizze stúdzje ûnderstreket de earnst en ympact fan oanhâldende klachten oer wurchte op jonge leeftiid sûnder dat der in medyske of psychologyske ferklearring foar is, en lit gjin plak oer foar in negative hâlding foar dizze klachten.

Yn de algemiene diskusje wurde de konsekwinsjes fan de útkomsten fan dizze stúdzje besprutsen yn ferhâlding ta de literatuer en wurde der foarstellen dien foar de praktyk fan de bernedokter. It ûndersyk nei in ûnderlizzende pathology foar de klachten oer wurchte kin beheind wêze en moat sa gau as mooglik ôfrûne wurde om de ûnwissens net langer duorje te litten. De erkenning fan de realiteit fan de klachten, empaty foar de pasjint en in begryplike en dúdlike útlis foarmje de basis foar eltse medyske behanneling, mar krekt by dizze pasjinten foarmet de dúdlike útlis in cruciaal probleem. De diagnose PUF ferhâldt him ommers per definysje dreech mei foldwaande dúdlikens. In foarbyld fan in metafoar mei útlokjende en ûnderhâldende faktoaren kin de pasjint en de âlden mear ynsjoch jaan yn it mechanisme dat de grûnslach der fan foarmet. It moat de pasjint dúdlik wêze dat it lichem en de geast yn dizzen in folsleine ienheid foarmje.It werkennen fan foarsizzende faktoaren kin in soad betsjutte foar de behanneling dy’t spesifyk ôfstimd wurdt op de oanbelangjende pasjint. It primêre doel fan de behanneling is, dat de pasjint him net ysolearret, mar safolle as mooglik meidwaan bliuwt oan skoalle- en sosjale aktiviteiten.. Hjirby is it fan belang dat der ûnderskied makke wurdt tusken passive en relatyf aktive pasjinten, om’t guon oanfitere en oaren krekt ôfremme wurde moatte. Om goed mei de ynterpretaasjes en attribúsjes fan de klachten om leare te gean, is kognitive gedrachs-terapy ek by jongerein in oantoande effektive foarm fan help.Dizze terapy kin lykwols allinne kâns fan slagjen ha as de pasjint gjin wjerstân tsjin in psychologyske benadering hat. Eltse behanneling moat ôfstimd wurde op de mooglikheden fan thús en skoalle. Hjirfoar is in struktureel multidisciplinair oerlis mei skoalle en thús needsaaklik binnen de romtes dy’t it medysk beropsgeheim en de learplichtwet biede.

Oerset troch : Hindrik van der Meer
Beitske van der Meer-Stavenga

Dankwoord

Op deze laatste bladzijden wil ik graag de mensen bedanken die op verschillende manieren hebben bijgedragen aan het tot stand komen van mijn proefschrift.

Allereerst Helene, moeder van onze vier kinderen met een toenemende schare omazeggers. Jij hebt mij altijd de ruimte gegeven om mij helemaal op mijn werk te kunnen concentreren, naast me, achter me en als het nodig was pal voor me. Zonder jou zou het met mij nooit zo goed gegaan kunnen zijn en zou ik nooit aan dit onderzoek begonnen zijn.

Wietse, Gerben en Elise, (co)promotor(en). Vanaf het allereerste moment dat ik bij jullie in het Wilhelmina Kinderziekenhuis kwam met de vraag of ik in 'de herfst van mijn kinderartsenbestaan' nog wetenschappelijk onderzoek zou kunnen doen naar aanhoudende onverklaarde lichamelijke klachten bij kinderen, waren jullie enthousiast en meer dan behulpzaam. Mijn niet academische denktrant werd altijd met welwillendheid in meer gangbare banen geleid. Ik heb me bij jullie thuis gevoeld en vind het oprecht jammer dat het nu is afgelopen. Jullie stimulerende altijd weer positieve reacties hebben mij veel meer gegeven dan de resultaten van dit boekje ooit kunnen tonen.

Cuno Uiterwaal. De manier hoe jij mij bij het opzetten van het databestand en de analyses hebt geholpen zijn onmisbaar geweest voor mij. Nooit heb ik tevergeefs om je hulp gevraagd als ik er alleen niet uit kwam. Altijd antwoordde je per ommegaande met E-mailtjes hoe ik stap-voor-stap in het SPSS-programma moest klikken om uit de problemen te komen.

De productie van de videofilm werd mogelijk gemaakt door een financiële bijdrage van de Rotaryclub afdeling Hilversum-West. Ik ben daar dankbaar voor.

VNO-Chrover. Gijs Bleijenberg, dank voor de mogelijkheden om bij de meetings in Nijmegen kennis en ervaring te mogen delen. De lange reis vanuit het Friese was nooit voor niets. Ik hoop dat ik als gepensioneerde welkom blijf.

In de praktijk blijkt het erg moeilijk om voor een onderzoek voldoende patiënten te kunnen includeren. Ik ben het dertigtal kinderartsen uit de verschillende ziekenhuizen in ons land zeer dankbaar voor het motiveren van hun patiënten om aan het onderzoek mee te doen.

Voor de patiënten was het een hele opgave om gedurende een jaar lang elke 3 maanden weer opnieuw vragenlijsten in te vullen en naar mij terug te sturen. Ze vonden het onderzoek belangrijk genoeg en hebben enthousiast mee gedaan. Mijn dank is groot.

Stefan van Geelen. Met plezier denk ik aan de samenwerking in ons ‘follow-up stukje’. Twee promovendi, jij met een hele toekomst voor je en ik met een toekomst achter me. Het was mooi om vanuit verschillende invalshoeken naar moeheid te kijken.

Lidewij Knook. Jouw data van de slaap van gezonde adolescenten lagen sluimerend te wachten om verder geanalyseerd te worden. Dank dat we ze konden gebruiken als controles voor ons ‘slaap stukje’.

Liz Walker, Engelse gastdochter. Dank voor je ondersteuning bij het leesbaar maken van mijn Engels voor native speakers..

Hindrik en Beitske van der Meer, doarpgenoaten. Tige tank foar de oersetting fan de gearfetting yn it Frysk.

Gerrit Peet, zwager. Al heel jong kwam je in ons gezin en werd je ‘mijn grote broer’, die de weg voor mij naar het gymnasium, de universiteit en het studentenleven vanzelf sprekend liet zijn. Je vertrouwde mij direct na mijn artsexamen de waarneming in je huisartsenpraktijk toe.

Anneke Bulk- Bunschoten, oudste vriendin. Vanzelfsprekend vroeg ik je mijn paranimf te willen zijn. Op ons zesde levensjaar leerden we lezen en schrijven van jufrouw Eickelenberg in een klas van 54 kinderen. Vanaf toen hebben we veel dierbare herinneringen. Zonder jou zou ik nooit zo snel zijn afgestudeerd en jouw promotie in 2003 was voor mij een stimulans.

Melle Jetze Bakker, oudste zoon. Ik ben er groots op dat je mede namens Mama, Wiebe, Hylke en Itha mijn paranimf wil zijn. Jullie zijn immers het mooiste wat mij is toebedeeld.

Curriculum Vitae

Robert Jan Bakker werd op 3 februari 1944 te Amsterdam geboren als zoon van Jan Bakker en Cecilia Robijns. In 1963 behaalde hij het eindexamen Gymnasium bèta op het Vondel Gymnasium te Amsterdam. In 1971 beëindigde hij zijn studie met het artsexamen aan de Gemeentelijke Universiteit (nu UvA). Tijdens de studieperiode roeide hij niet onverdienstelijk bij de ASRV Nereus. Na een assistentschap Interne Geneeskunde in het Burgerziekenhuis te Amsterdam en enkele waarnemingen voor huisartsen in verschillende delen van het land, begon hij in 1972 met de opleiding tot kinderarts in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider dr. G.A. Fehmers). Van 1 september 1976 tot 1 april 2007 werkte hij als kinderarts in het Sint Antonius ziekenhuis (nu Antonius ziekenhuis) te Sneek. In deze periode was hij tevens 26 jaar als staflid verbonden aan “it Mearke”, een kinderdagcentrum voor jonge kinderen met een ontwikkelingsachterstand te Bolsward en 8 jaar aan de Cluster 4 school van het Medisch Kindertehuis “Mooi Gaasterland” te Rijs. Als vertrouwensarts voor de provincie Friesland was hij van 1976 tot 1985 aangesteld bij het Bureau Vertrouwensartsen inzake Kindermishandeling en van 2004 tot 2009 bij het Advies en Meldpunt Kindermishandeling.

Hij was lid van verschillende landelijke, provinciale en gemeentelijke commissies op het gebied van opvoedingsondersteuning en seksuele kindermishandeling en medeauteur van het rapport van de Gezondheidsraad ’Medische aspecten van seksueel misbruik van kinderen.’ Daarnaast publiceerde hij over huiselijk geweld, meersporenbeleid bij incest en signalering van kindermishandeling.

In 1999 is bij hem bij een skiongeval een Carotis dissectie ontstaan, waarna hij tijdelijk niet meer verantwoord dienst kon doen gedurende de nachten en weekeinden. Vanaf die periode heeft hij de kindergeneeskunde alleen nog poliklinisch uitgeoefend en is hij gestart met het opzetten van een onderzoek dat uiteindelijk tot een promotie moest leiden.

Rob is sinds 1970 gehuwd met Helene, dochter van Cor Renes en Anna van Buren. Hij heeft 1 dochter en 3 zoons en op het moment van schrijven 3 kleinkinderen.