From prevalence to predictors of fatigue in neuromuscular disorders

the building of a model

Illustratie omslag: Karokoram Highway, Hussaini, Pakistan (J.S. Kalkman)
Cover design: Carl Looijen

Printed by Ponsen & Looijen BV, Wageningen. The Netherlands.
ISBN-10: 90-9020984-0
ISBN-13: 978-90-9020984-5

From prevalence to predictors of fatigue in neuromuscular disorders

the building of a model

Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen

Proefschrift
ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus prof.dr. C.W.P.M. Blom
volgens besluit van het College van Decanen in het openbaar te verdedigen
op dinsdag 31 oktober 2006 des namiddags om 1.30 uur precies

door **Johanna Sibina Kalkman**
geboren op 27 december 1966 te Den Helder

Promotores:
Prof.dr. G. Bleijenberg
Prof.dr. B.G.M. van Engelen
Prof.dr. M.J. Zwarts

Manuscriptcommissie:
Prof.dr. J.W.M. van der Meer, voorzitter
Prof.dr. L. Fasotti
Prof.dr. A.C.H. Geurts

Paranimfen:
Mw.drs. K.M. Landsbergen
Mw. M.I. Roddeman-Kalkman

The work presented in this thesis is part of the research program of the Institute for Fundamental and Clinical Human Movement Sciences (IFKB).

The studies were supported by the Prinses Beatrix Fonds (grantnr. Mar 00-0121), and the Health Research and Developmental Council of the Netherlands (NWO ZON-MW, grantnr. 940-38-024).

De publicatie van dit proefschrift kwam mede tot stand dankzij financiële steun van de afdeling Medische Psychologie van het Universitair Medisch Centrum St. Radboud, Beenhakker Revacore BV en Organon Nederland BV.

een brug naar morgen

dankzij mijn ouders

CONTENTS

CHAPTER 1 9
Introduction

CHAPTER 2 17
Fatigue in neuromuscular disorders

CHAPTER 3 25
Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-I patients

CHAPTER 4 35
Psychiatric disorders appear equally in patients with myotonic dystrophy, facioscapulohumeral dystrophy, and Hereditary Motor and Sensory Neuropathy type I

CHAPTER 5 45
Ambulatory disabilities and the use of walking aids in HMSN-I patients

CHAPTER 6 57
Experienced and physiological fatigue in neuromuscular disorders

CHAPTER 7 73
Determinants of experienced and physiological fatigue in patients with facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I

CHAPTER 8 89
Pain and the relation with fatigue in patients with facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I

CHAPTER 9 97
Influence of relatives on fatigue experienced by patients with facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I

CHAPTER 10 107
The development of a model of fatigue in neuromuscular disorders: a longitudinal study

CHAPTER 11 123
General discussion

SUMMARY 143
SAMENVATTING 147

LIST OF PUBLICATIONS 151
LAATSTE WOORD 155
CURRICULUM VITAE 159

CHAPTER 1

General Introduction

General Introduction

Fatigue is a common symptom in a number of (chronic) neurological disorders such as multiple sclerosis, Parkinson's disease and stroke (1-7). It was found in patients with these diseases that the experience of severe fatigue can be a major determinant of disability and influences the quality of life (8-9). Fatigue in neuromuscular disorders has received surprisingly little attention, although the clinical experience of our research group has indicated that many patients with neuromuscular disorders report fatigue and consider it an important problem (10).

Expert Centre Chronic Fatigue

The Expert Centre Chronic Fatigue is a multidisciplinary collaboration of internists, virologists, neurologists, neurophysiologists, neuroscientists, oncologists, and psychologists from several departments of the Radboud University Nijmegen Medical Centre. This centre has studied chronic fatigue since 1990, not only in chronic fatigue syndrome, but also in multiple sclerosis, after cancer, and in several other (chronic) diseases. A multidimensional assessment method was developed and used to create and test models of perpetuating factors in chronic fatigue syndrome and multiple sclerosis. These models served as guidelines for developing specific treatment interventions

Neuromuscular Centre Nijmegen

The Neuromuscular Centre Nijmegen investigates basic molecular, histological, genetic and physiological mechanisms underlying the common neuromuscular and neurometabolic disorders like myotonic dystrophy, facioscapulohumeral dystrophy, hereditary motor and sensory neuropathies, myositis, and mitochondrial myopathies, starting from the clinical phenotype. Research has been focused on various measurement methods and underlying aspects of muscle (physiological) fatigue in recent years.

The collaboration between the Expert Centre Chronic Fatigue and the Neuromuscular Centre Nijmegen combines the expertise of two multidisciplinary research groups with predictors of fatigue in neuromuscular disorders.

Experienced fatigue

Asking patients to describe fatigue will lead to a variety of descriptions: e.g. exercise intolerance, weakness, sleepiness or exhaustion. This means that the term fatigue may be confusing, especially when used in the context of neuromuscular disorders - in which weakness is usually the main symptom - and so the definitions and assessment of the symptom of fatigue are complicated as a consequence. Krupp has defined experienced fatigue as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion (1). It is not the same as muscle weakness or muscle fatigability.

Fatigue as experienced by the patient is one of the symptoms most frequently presented to the treating physician, but most physicians do not know how to handle a symptom of this kind. Furthermore, they do not know how to estimate the severity of the problem and assessment instruments are useful as a consequence. Fatigue consists of several dimensions, which means it is also necessary to assess the other dimensions. A multidimensional assessment method was

developed, therefore, and was tested and validated in cross-sectional and prospective studies of several chronic disorders (11-15).

The following relatively independent dimensions appeared to make a contribution to the experience of fatigue: functional impairment in daily life, physical activity, psychological distress, sleep disturbances, concentration problems, social functioning, social support, sense of control over fatigue (self-efficacy), attributions of the possible cause of fatigue, and pain. The question where each condition is concerned, is which dimension contributes to experienced fatigue and to what degree.

Since different modes of assessment may yield different results, it is appropriate to measure each dimension by a variety of methods and different modalities of assessment are used within the multidimensional assessment method (16), including self-report questionnaires, standardised sleep and complaint diaries, neuropsychological and behavioural tests, and a motion-sensing device (actometer) (Table 1.1).

This multidimensional assessment method made it possible to develop and test a model of perpetuating factors of fatigue in chronic fatigue syndrome (17), which model became the basis of the treatment of chronic fatigue syndrome. The same method enabled the development of a model and subsequently a treatment for fatigue in cancer survivors (13).

TABLE 1.1. Types of fatigue and its assessment

Type of fatigue		**Assessment**
Experienced fatigue	**Fatigue severity**	**Self-report**
Dimension:	Functional impairment in daily life	Self-report
	Physical activity	Self-report
		Actometer
	Psychological distress	Self-report
	Sleep disturbances	Self-report
	Concentration problems	Self-report
		Neuropsychological tasks
	Social functioning	Self report
	Social support	Self report
		Report of relatives
	Self-efficacy	Self-report
	Causal attribution	Self-report
	Pain	Self-report
Physiological fatigue	**Localization**	**Assessment**
Central fatigue	Brain	Twitch interpolation technique
	Spinal cord	Twitch interpolation technique
Peripheral fatigue	Peripheral nerve	EMG
	Neuromuscular junction	EMG
	Muscle	EMG

Physiological fatigue

Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force and is divided into peripheral and central components (18). The loss of force-producing capacity can have both a peripheral and a central origin (and simultaneously), because muscles do not function automatically, but are activated by the central and peripheral nervous system (Table 1.1).

Physiological measurements were used to determine peripheral fatigue and central fatigue. The experimental design was used in previous studies of peripheral and central aspects of fatigue in healthy subjects (19-20) and the assessment of the central part of fatigue was achieved by means of the twitch interpolation technique (21).

In short, subjects made a 2-minute sustained maximal voluntary contraction of the biceps brachii muscle. Electrical stimulation was applied before, just after and every 15 seconds during maximal voluntary contraction (MVC). Each stimulus event consisted of 5 applications of a 5-pulse 100 Hz stimulus train to the motor point.

The difference in force response during rest before and after sustained MVC was used as a measure for peripheral fatigue and superimposed force responses during MVC indicated the level of central activation failure. It is a fact that if voluntary muscle activation is optimal, electrical stimulation on the muscle will not induce an increase in force. If a failure of voluntary central drive is present, however, electrical stimulation will lead to a superimposed force response.

Despite increasing knowledge of the physiology of peripheral and central fatigue, most studies are conducted in healthy controls and so relatively little is known about these aspects of physiological fatigue in patients with neuromuscular disorders. This thesis provides the opportunity, therefore, to measure experienced fatigue and physiological fatigue simultaneously and to assess their interrelationships.

Fatigue in neuromuscular disorders

Although clinical research shows an increasing interest in aspects of quality of life, experienced fatigue is only included sporadically, which is also the case in studies of neuromuscular disorders unfortunately.

Within the group of neuromuscular disorders, fatigue has mostly been described in patients with post-polio syndrome (22,23), myasthenia gravis (24), and immune mediated neuropathies like Guillain-Barré syndrome (25). Fatigue usually starts at the onset of the disease in the case of the last disorder and often stays present for months, in spite of recovery of the nervous system. Literature is lacking about the relationship between experienced fatigue and physiological fatigue.

Now that reliable psychological and clinical neurophysiological techniques are available, a multidisciplinary approach may contribute to the elucidation of fatigue in patients with neuromuscular disorders and this is what we have tried to do in this thesis.

This thesis concerns three genetically well defined, homogeneous, and large populations of patients with relatively common neuromuscular disorders, namely facioscapulohumeral muscular dystrophy (FSHD), adult-onset myotonic dystrophy (MD) and hereditary motor and sensory neuropathy type I (HMSN) (26-28). FSHD is an autosomal dominantly inherited myopathy, initially characterized by weakness and atrophy in facial, upper arm, and shoulder girdle muscles, often progressing to affect peroneal and pelvic girdle muscles (29).

MD is the most common form of muscular dystrophy and is also an autosomal dominant hereditary multisystemic disease characterized by myotonia, muscle weakness and atrophy, cataracts, cardiac abnormalities, excessive daytime sleepiness, and disorders of other systems such as the endocrine system, gastrointestinal tract, skin and bone (30). HMSN, also known as Charcot-Marie-Tooth disease, forms a heterogeneous group of slowly progressive heritable disorders of the peripheral nervous system (31).The most common form is type I, the clinical features of which include a symmetrical distal muscle weakness and atrophy, and areflexia and sensory impairment with distal loss of touch, pain, vibration and joint position sense. This thesis, therefore, compares patients with three different neuromuscular disorders, including a myopathy, a multisystem disorder and a neuropathy.

Towards a model of fatigue in neuromuscular disorders

In view of the fact that fatigue has several dimensions, it is important to find factors that perpetuate fatigue in the three neuromuscular disorders. Which factors are determinants of fatigue, and how are they related? Patients with neuromuscular disorders perceive various symptoms produced by the pathophysiology of the disorder and affected either directly or indirectly via functional limitations or psychological distress, while patients' perceptions or reports of symptoms can be influenced by different factors, such as psychiatric comorbidity and the support of close relatives. Functional status refers to the consequences of the disorder on a person's ability to perform functions that are part of everyday life, including physical, social, role, and mental functions.

If we know which factors have predictive value for continuation of the experience of fatigue, we can develop a model on which interventions can be based. A longitudinal design was used to investigate which factors may be predictors of fatigue and we also investigated whether psychiatric comorbidity has a place in the model of perpetuating factors, which we also did for the role of the support of close relatives and the relationship with patients' experienced fatigue.

The various dimensions and the contribution of each dimension to fatigue were investigated, to enable us to include or exclude a dimension in the final model of fatigue in these disorders. Structural equation techniques, also referred to as "causal modelling" were used to develop and test a model of fatigue in neuromuscular disorders, with the objective of developing a theoretically and data-driven model that can be used for the selection and development of treatment strategies to reduce fatigue.

Outline of this thesis

After the introduction of the problem of fatigue (Chapters 1 and 2), we assess the prevalence of experienced fatigue in large groups of patients with three relatively common neuromuscular disorders, namely FSHD, MD, and HMSN (Chapter 3). We used a validated fatigue questionnaire with an empirically derived cut-off score to assess experienced fatigue.

In Chapter 4 we assess the relationship between psychiatric comorbidity, severe experienced fatigue, and muscle strength in these patients, as a consequence of which we investigated the presence of current and lifetime psychiatric comorbidity by the use of a structured clinical interview and self-reported questionnaires. Furthermore, we investigated the relationship

between experienced fatigue and ambulatory and mobility-related problems, and the use of walking aids (Chapter 5).
The contribution of physiological factors to fatigue may be particularly relevant in neuromuscular disorders, however, and Chapters 6 and 7 present the relationship between experienced and physiological fatigue. We studied different types of fatigue (experienced fatigue and physiological fatigue) using a multidimensional assessment method to determine which dimensions were related to experienced fatigue and which to physiological fatigue.
In Chapter 8 we explore the relationship between pain and experienced fatigue in FSHD, MD, and HMSN, investigating the presence, localization and other characteristics of pain in these disorders and its relationship with experienced fatigue.
Chapter 9 addresses the influence of close relatives on the patient's experienced fatigue, the responses of these relatives, and the relationship between the responses of the close relatives and the degree of the patient's experienced fatigue.
In Chapter 10 the focus is on the development of a model of perpetuating factors, using longitudinal data for a large cohort of patients with three neuromuscular disorders. The model is first tested in the group a whole and we subsequently attempt to develop separate models for the three neuromuscular disorders.
In the final chapter of this thesis (Chapter 11), the general discussion addresses the main findings and clinical implications.

REFERENCES

1. Krupp LB, Fatigue. Butterworth Heinemann. 2003.
2. Ford H, Trigwell P, Johnson M. The nature of fatigue in Multiple Sclerosis. J Psychosom Res 1998; 45: 33-38.
3. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. Mov Disord 1999; 14: 237-241.
4. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology 1993; 43: 2016-2018.
5. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord 2001; 16: 190-196.
6. Van der Werf SP, van den Broek HL, Anten HW, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur Neurology 2001; 45: 28-33.
7. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. Arch Phys Med Rehabil 1999; 80: 173-178.
8. Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand 2003; 107: 1-6.
9. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994; 21: 9-14.
10. van Engelen BGM, Kalkman JS, Schillings ML, van der Werf SP, Bleijenberg G, Zwarts MJ. Moeheid bij neuromusculaire aandoeningen. Ned Tijdschr Geneeskd 2004; 148(27): 1336-1341.
11. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.

12. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
13. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients : a cross-sectional study. Ann of Oncol 2002 ; 13: 589-598.
14. Werf SP van der. Determinants and consequences of experienced fatigue in chronic fatigue syndrome and neurological conditions [dissertation]. Nijmegen:University Nijmegen, 2003.
15. Vries M de, Soetekouw PM, Meer van der JW, Bleijenberg G. Fatigue in Cambodia veterans. QJM 2000; 93: 283-289.
16. Eiffert GH, Wilson PH. The triple response approach to assessment: a conceptual and methodological reappraisal. Behav Res Ther 1991; 29: 283-292.
17. Vercoulen JH, Swanink CM, Galama JM et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: Development of a model. J Psychosom Res 1998; 45: 507-517.
18. Bigland-Ritchie B, Jones DA, Hosking GP, Edwards RH. Central and peripheral fatigue in sustained maximum voluntary contractions of human quadriceps muscle. Clin Sci Mol Med 1978; 54: 609-614.
19. Kent-Braun JA. Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. Eur J Appl Physiol Occup Physiol 1999; 80: 57-63.
20. Schillings ML, Hoefsloot W, Stegeman DF, Zwarts MJ. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. Eur J Appl Physiol 2003; 90: 562-568.
21. Shield A, Zhou S. Assessing voluntary muscle activation with the twitch interpolation technique. Sports Med 2004; 34: 253-267.
22. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
23. Sunnerhagen KS, Grimby G. Muscular effects in late polio. Acta Physiol Scand 2001; 171 (3); 335-340.
24. Paul RH, Cohen RA Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
25. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
26. Emery AEH. Diagnostic criteria for neuromuscular disorders, 2nd edition. London: Royal Society of Medicine Press, 1997.
27. Engel AG, Franzini-Armstrong C. Myology, 3rd edition. New York: McGraw-Hill, 2004.
28. Dyck PJ, Thomas PK. Peripheral neuropathy, 4th edition. London: Saunders, 2005.
29. Padberg GW, Lunt PW, Koch MC, Fardeau M. Diagnostic criteria for facioscapulohumeral muscular dystrophy. Neuromusc Disord 1991; 1(4): 231-234.
30. Harper PS. Myotonic dystrophy, 3rd version. London: Harcourt Publishers Ltd, 2001.
31. Gabreels-Festen AA, Bolhuis PA, Hoogendijk JE, Valentijn LJ, Eshuis EJ, Gabreels FJ. Charcot-Marie-Tooth disease type 1A: morphological phenotype of the 17p duplication versus PMP22 point mutations. Acta Neuropathol (Berl) 1995; 90(6): 645-649.

CHAPTER 2

Fatigue in neuromuscular disorders

This chapter was published as:
Van Engelen BGM, Kalkman JS, Schillings ML, van der Werf SP, Bleijenberg G, Zwarts MJ. Moeheid bij neuromusculaire aandoeningen.
Nederlands Tijdschrift voor Geneeskunde, 2004; 148(27): 1336-1341.

ABSTRACT

Chronic fatigue is a symptom of diseases such as cancer, multiple sclerosis, Parkinson's disease and cerebrovascular disorders. Fatigue can also be present in people with no demonstrable somatic disease. If certain criteria are met, chronic fatigue syndrome can be diagnosed. Fatigue is a multi-dimensional concept with both physiological and psychological aspects. The 'Short Fatigue Questionnaire' consisting of 4 questions is a tool to measure the level of experienced fatigue with a high degree of reliability and validity.
Within the group of patients with neuromuscular disorders, fatigue has been reported in patients with post-polio syndrome, myasthenia gravis and Guillain-Barré syndrome. The percentage of neuromuscular patients suffering from severe fatigue (64%) is similar to that of patients with multiple sclerosis, a disease in which fatigue is an acknowledged symptom.
Now that reliable psychological and clinical neurophysiological techniques are available, a multidisciplinary approach to fatigue in patients with well-defined neuromuscular disorders may contribute towards the elucidation of the pathophysiological mechanisms of chronic fatigue, with the ultimate goal to develop methods of treatment for fatigue in neuromuscular patients.

INTRODUCTION

Fatigue is a universal and daily phenomenon. In the general practitioner's office, symptoms of fatigue are ranked third on the list of most reported problems (1).The symptom of fatigue, however, covers a difficult multidimensional concept and therefore creates a complex problem for the physician.

Fatigue as a chronic symptom is a well-known manifestation of a number of somatic disorders, like cancer, multiple sclerosis, Parkinson's disease and cerebrovascular disorders (Table 2.1). It also occurs as a side-effect of medication like β-blockers. Fatigue has been described in depression and during stress. There also is a group of severely fatigued patients that do not have a somatically demonstrable disease. If fatigue exists for more than 6 months and patients fulfill a number of additional criteria (Table 2.2), the disorder is diagnosed as chronic fatigue syndrome (CFS) (2). It is estimated that about 30,000 to 40,000 people suffer from CFS in the Netherlands (3). It is less well known that chronic fatigue also often occurs in neuromuscular disorders and that it has a considerable impact on these patients. Citing a neuromuscular patient: "Personally I consider fatigue as a more severe problem than the measurable somatic problems and handicaps. Fatigue makes me miss several things, whereas I could learn to live with the somatic handicaps. Despite my somatic problems I could fully function in society, if only the problem of fatigue was solved."

TABLE 2.1. Percentage of patients with several disorders experiencing severe fatigue.

Disorder	Percentage of severely fatigued patients
Cancer (during treatment)	75-99 [4,5]
Multiple sclerosis	57-97 [4,6]
After cerebrovascular accident	51 [7]
Chronic pancreatitis	73 [7]
Post polio syndrome	80 [4]
Parkinson's disease	65 [4]
Systemic lupus erythematosus	80 [4]
Myasthenia gravis	82 [8]
Guillain-Barré syndrome	81-86 [9]

In the fundamental sciences, especially neurobiology, fatigue has been defined as a time-related force decline (10,11). In clinical medicine fatigue has not been investigated thoroughly until recently, possibly because the term was regarded subjective and was not well-defined (12). Now that we have a better insight into different aspects of chronic fatigue and we can measure these reliably, subjective feelings can be studied scientifically. Therefore, researchers and clinicians more and more see that fatigue is a problem worth the study (4,7).

This chapter describes the term fatigue and how it can be measured and reviews the literature about fatigue in neuromuscular disorders.

TABLE 2.2. Criteria for chronic fatigue syndrome (2)

To diagnose chronic fatigue syndrome the following criteria should be fulfilled
Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset (has not been lifelong) and lasts for 6 or more consecutive months
Fatigue is not the result of ongoing exertions
Fatigue is not substantially alleviated by rest
Fatigue results in substantial reduction in previous levels of occupational, educational, social, or personal activities
Four or more of the following symptoms are concurrently present for ≥ 6 months
Impaired memory or concentration
Sore throat
Tender cervical or axillary lymph nodes
Muscle pain
Multi-joint pain
New headaches
Unrefreshing sleep
Post-exertion malaise

Experienced fatigue

Asking patients or physicians to describe fatigue will lead to a variety of descriptions: e.g. sleepiness, weakness, exercise intolerance or exhaustion. Thus, the term fatigue may be confusing, especially when used in the context of neuromuscular disorders, in which weakness is usually a main symptom. This complicates the definition, diagnosis and treatment of the symptom of fatigue.

Medical literature usually defines fatigue in the sense of 'experienced fatigue': an overwhelming sense of tiredness, lack of energy and feeling of exhaustion (4,7,13,14). A problem arises in discriminating the level of fatigue between different individuals. Everyone knows the feeling of fatigue, but do we mean the same thing? In order to compare levels of fatigue between subjects, fatigue should be quantified. For physicians this has practical implications, because they often need to evaluate the seriousness of the sign. This may be important to predict other symptoms or consequences of the disease, like the need for medical supplies or a reduction in working hours (15). Experienced fatigue is a concept with both psychological and physiological dimensions. For example the psychological factors well-being, concentration, attributions and social functioning may all influence experienced fatigue (16) (Table 2.3).

Experienced fatigue can best be quantified with questionnaires. The Checklist Individual Strength (CIS) (17) contains an eight-item subscale fatigue. It is used both for scientific research and for patient care. For clinical practice also the Abbreviated Fatigue Questionnaire (AFQ) may be used (18,19). This is a shortened version of the CIS, which measures fatigue with four items. It has both a good reliability and validity and has been developed to use in the general practitioner's office.

Physiological fatigue

In physiology, fatigue is usually defined as the loss of voluntary force-producing capacity during exercise (20). Physiological fatigue is not necessarily accompanied by experienced fatigue, nor

vice versa. The loss of force producing capacity can both (and simultaneously) have a peripheral and a central origin because muscles do not function autonomically, but are activated by the nervous system (Table 2.3).
Fatigue has mostly been studied at the peripheral level, that is in the muscle tissue. Peripheral fatigue is mainly ascribed to changing intracellular ion levels having a negative effect on contractile force (21-23). During peripheral fatigue, accumulation of lactate and extracellular potassium, together with a lowering of the pH, influence membrane excitability (24). Therefore, muscle fiber conduction velocity reflects the peripheral situation. With the multi-channel electrode grids developed at the Department of Clinical Neurophysiology in Nijmegen muscle fibre conduction velocity can be assessed quite easily (25). The most direct measure of peripheral fatigue, however, is the different force response to artificial electrical stimulation during rest after exercise compared to before. This directly shows the loss of force produced by the muscle tissue after constant input into the muscle.

TABLE 2.3. Dimensions possibly influencing experienced fatigue.

Type of fatigue	**Location**
Physiological	
Central fatigue	Brain
	Spinal cord
	Peripheral nerve
Peripheral fatigue	Neuromuscular transition
	Muscle
Psychological	
Concentration	
Restrictions in daily functioning	
Physical activity	
Attributions about fatigue (e.g. attitude, self-efficacy)	
Social support	
Psychological well-being	
Sleep disturbances	

Central fatigue, the decrease of voluntary activation of the muscle by the nervous system, nowadays gains interest. A muscle receiving suboptimal input from the nervous system will not show its maximal force capacity. In the case of sub-maximal central activation, central activation failure (CAF) is said to be present. An increase of CAF during exercise is called central fatigue.
Sub-maximal voluntary drive may have several causes, like a lack of motivation or exhaustion of cortical neurons in the motor cortex. Usually, CAF is determined with a version of the so called twitch-interpolation technique (26). Subjects are instructed to make a maximal voluntary contraction (MVC) of a specific muscle. During MVC, artificial electrical stimulation is applied on the motor nerve or motor endplate. If voluntary central drive is optimal, this will not lead to additional force production. However, if voluntary activation is sub-maximal, electrical stimulation results in an increase of force. Thus, in this case CAF can be shown. With this

technique, CAF can be quantified and its change over time (central fatigue) may be studied, but it cannot discriminate between the different causes of CAF.
Combining data about central and peripheral aspects of fatigue will lead to a more profound insight into the relative contributions of these aspects to physiological fatigue.

Fatigue in neuromuscular disorders

Because experienced fatigue has direct consequences for the quality of life, questionnaires like the CIS can be used in studies in which the quality of life is the main research topic (18). Although clinical research shows an increasing interest in aspects of quality of life, experienced fatigue is only sporadically included. This unfortunately is also the case for studies into neuromuscular disorders. In a number of other neurological disorders, like multiple sclerosis or Parkinson's disease, however, fatigue is well-known and accepted as a disease related symptom(6,13,27,28) (Table 2.1).
Despite the many different neuromuscular disorders, only a limited number of symptoms occurs. Muscle weakness is the most typical one. Other symptoms are pain, muscle loss, involuntary movements, myotonia, and contractures (29). Experienced fatigue is not the same as weakness; fatigue is an independent symptom. Patients having fatigue without weakness usually do not have a known neuromuscular disorder (30). In contrast, fatigue is not often recognized as a problem in neuromuscular disorders accompanied by weakness (31).
A number of patients with specific neuromuscular disorders like metabolic or mitochondrial disorders, however, do not show muscle weakness, but do show fatigue in the sense of exercise intolerance. Besides, some types of patients experience both muscle weakness and fatigue, like for example the patient cited above. A possible explanation is that the weak or atrophic muscles have to function at their (e.g. metabolic) limits (30). For these patients, daily life is so demanding that we could consider them top sportsmen in daily life. This type of fatigue has not yet been studied well.
Within the group of neuromuscular disorders, fatigue has mostly been described in patients with postpolio syndrome (32,33), myasthenia gravis (8), and immune mediated neuropathies like Guillain-Barré syndrome (9). In the last disorder, fatigue usually starts at the onset of the disease and often stays present for months in spite of total recovery of the peripheral nervous system. In myasthenia gravis peripheral fatigue has been studied and explained only part of the experienced fatigue (8).
As a first investigation preceding the extensive study presented in the next chapter, our group has compared experienced fatigue, functional limitations, psychological well-being and depression in 64 consecutive patients with a neuromuscular disorder visiting the outpatient clinic of our hospital and in 94 patients with multiple sclerosis (34). Sixty four % of the patients with a neuromuscular disorder and 57 % of those with multiple sclerosis experienced severe fatigue. Thus, experienced fatigue appears equally in patients with neuromuscular disorders and multiple sclerosis. Though, in multiple sclerosis fatigue is generally accepted, whereas it is not in neuromuscular disorders. To optimize care for patients with neuromuscular disorders it is important to recognize these high percentages of fatigue and to understand the underlying pathophysiological mechanisms.

REFERENCES

1. Lamberts H. In huis van de huisarts. Verslag van het Transitieproject . Lelystad: Meditekst, 1991.
2. Fukuda K, Straus SR, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definitions and study. International Chronic Fatigue Syndrome Study Group. Ann Intren Med 1994; 121(12): 953-959.
3. Health Council of the Netherlands. Het chronische- vermoeidheidssyndroom. [Chronic Fatigue Syndrome]. 2005, Jan 25. Report No: 2005/02.
4. Krupp LB, Fatigue. Butterworth Heinemann. 2003.
5. Servaes P, Verhagen S, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. Eur J Cancer 2002; 38: 27-43
6. Werf SP van der. Determinants and consequences of experienced fatigue in chronic fatigue syndrome and neurological conditions [dissertation]. Nijmegen:University Nijmegen, 2003.
7. Bleijenberg G. De ene vermoeidheid is de andere niet. Nijmegen:UB Nijmegen, 2003.
8. Paul RH, Cohen RA Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
9. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune-mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
10. Gandevia SC, Enoka RM, McComas AJ, Stuart DG, Thomas CK. Fatigue, neural and muscular mechanisms. New York: Plenum Press. 1995.
11. Hill AV. The heat production in prolonged contractions of an isolated frog's muscle. J Physiol 1913; 47: 305-324.
12. Lou J, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinsons's disease. Mov Disord 2001; 16: 190-196.
13. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology 1993;43:2016-8.
14. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. Mov Disord 1999; 14: 237-241.
15. Pawlikowska T, Chadler T, Hirsch SR, et al. Population based study of fatigue and psychological distress. BMJ 1994; 308: 763-766.
16. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
17. Beurskens AJ, Bultmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occup Environ Med. 2000; 57: 353-37.
18. Alberts M, Smets FMA, Vercoulen JHMM, Garssen B, Bleijenberg G. 'Verkorte vemoeidheids-vragenlijst': een praktisch hulpmiddel bij het scoren van vermoeidheid. Ned Tijdschr Geneeskd 1997; 141: 1526-1530.
19. Alberts M, Vercoulen JH, Bleijenberg G. Assessment of fatigue. The practical utility of the subjective feeling of fatigue in research and clinical practice.
    In: Vingerhoets A,ed. Assessment in behavioural medicine. Brunner Routledge, 2001: 301-327.
20. Bigland-Ritchie B, Jones DA, Hosking GP, et al. Central and peripheral fatigue in sustained maximum voluntary contraction of human quadriceps muscle. Clin Si Mol Med 1978; 54: 609-614.
21. Allen DG. Skeletal muscle function: role of ioninc changes in fatigue, damage and disease. Clin Exp Pharmacol Physiol 2004; 31(8): 485-493.
22. Green HJ. Membrane excitability, weakness, and fatigue. Can J Appl Physiol 2004; 29: 291-307.
23. Vandenboom R. The myofibrillar complex and fatigue: a review. Can J Appl Physiol 2004; 29: 330-356.

24. Zwarts MJ, Stegeman DF. Multichannel surface EMG: basic aspects and clinical utility. Muscle Nerve 2003; 28: 1-17.
25. Zwarts MJ, Drost G, Stegeman DF. Recent progress in the diagnostic use of surface EMG for neurological diseases. J Electromyogr Kinesiol 2000; 10: 287-291.
26. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001; 81: 1725-1789.
27. Ford H, Trigwell P, Johnson M. The nature of fatigue in Multiple Sclerosis. J Psychosom Res 1998; 45: 33-38.
28. Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis: Current understanding and future directions. J Rehabil Res Dev 2002; 39: 211-24.
29. De Visser M,Vermeulen M, Wokke JHJ. Neuromusculaire ziekten. Maarsen: Elsevier/ Bunge. 1999.
30. Layzer RB. Asthenia and the chronic fatigue syndrome. Muscle Nerve 1998; 21: 1609-1611.
31. Chaudhuri A, Behan PO. Fatigue and basal ganglia. J Neurol Sci 2000; 179: 34-42.
32. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
33. Stibrant Sunnerhagen K, Grimby G. Muscular effects in late polio. Acta Physiol Scand 2001; 1771: 335-340.
34. Kalkman JS, van der Werf SP, van Engelen BGM, et al. Fatigue complaints are equally characteristic for neuromuscular diseases as for multiple sclerosis. Neuromuscul Disord 2002; 12 :779.

CHAPTER 3

Experienced fatigue in Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I patients

This chapter was published as:
Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I patients.
Journal of Neurology, Neurosurgery, and Psychiatry, *2005; 76: 1406-1409*.

ABSTRACT

Objectives

The primary object of this study was to assess the prevalence of experienced severe fatigue and its relation with functional impairments in daily life in a large sample of patients with relatively common types of neuromuscular disorders.

Methods

598 patients with a neuromuscular disorder (139 Facioscapulohumeral Dystrophy, 322 adult-onset Myotonic Dystrophy patients and 137 Hereditary Motor and Sensory Neuropathy type I patients) were studied. Fatigue severity was assessed with the Checklist Individual Strength (CIS-fatigue). Functional impairments in daily life were measured with the SF-36 health survey questionnaire (SF-36).

Results

The three different neuromuscular patient groups were similar with respect to age and gender. Severe experienced fatigue was reported by 61-74 percent of the patients. Severely fatigued neuromuscular patients had more problems with physical functioning, social functioning, mental health, bodily pain, and general health perception.

Conclusion

Severe fatigue is reported by the majority of patients with relatively common types of neuromuscular disorders. Because experienced fatigue severity is associated with the severity of various functional impairments in daily life, it is a clinically and socially relevant problem in this group of patients. There appeared to be several differences in relation with fatigue between the three neuromuscular disorders.

INTRODUCTION

Experienced fatigue has been defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion and is not the same as weakness (1). Fatigue is a common symptom in different neurological disorders such as multiple sclerosis, Parkinson's disease and stroke (1-7). In these patient populations it was found that the experience of severe fatigue can be a major determinant of disability and has influence on the quality of life. Surprisingly, fatigue in neuromuscular disorders has received very little attention so far. There are some studies in patients with various neuromuscular disorders. Paul et al showed that 82% of a group of myasthenia gravis patients reported fatigue as a regular symptom of their disease (8). A study of Berlly et al showed that 68% of a group of post-polio patients reported daily fatigue. Half of these fatigued patients noted that their fatigue had led to the need for assistance in daily life (9). In a group of immune-mediated polyneuropathies it was found that fatigue was a prominent and highly disabling symptom (10). Herlofson et al showed that fatigued patients with Parkinson's disease reported more problems in areas of functional limitations (11). Fisk et al found that fatigue has a significant effect on the general health status in patients with multiple sclerosis (12). The impact of fatigue in health related quality of life in patients with neuromuscular disorders has not been studied so far.

Clinical experience and preliminary findings of our research group indicated that also many patients with a neuromuscular disorder experience severe fatigue and consider it an important problem (13). Most psychological studies in neuromuscular disorders, however, have focused mainly on disability or loss of quality of life, and did not address the problem of experienced fatigue among different neuromuscular disorders (14-16). Currently, no cross-sectional study has compared the presence and severity of fatigue in various neuromuscular disorders using validated instruments.

This study concerns three genetically well defined, homogeneous, and large populations of patients with relatively common neuromuscular disorders, namely facioscapulohumeral muscular dystrophy (FSHD), adult-onset myotonic dystrophy (MD) and hereditary motor and sensory neuropathy type I (HMSN). FSHD is an autosomal dominantly inherited myopathy (17). MD is the most common form of muscular dystrophy and is an autosomal dominant hereditary multisystemic disease involving skeletal muscles, eye, heart, lungs, gastrointestinal tract, bone, skin, central nervous system and peripheral nervous system (18). HMSN type I is the most common genetic disorder affecting the peripheral nervous system (19-21). Thus, this study compares experienced fatigue in three different neuromuscular patient populations, including a myopathy, a multisystem disorder and a neuropathy.

Our research group has developed a multidimensional assessment method to measure fatigue in several chronic disorders (22-25). In this study we investigated besides fatigue severity the relation between fatigue and functional impairments in daily life.

Health-related quality of life scales, like the Short Form 36 (SF-36), might be useful to assess important domains of health and various aspects of impairment from the patient's perspective (26). We chose the SF-36 as the most widely used generic health related scale to evaluate the potential impact of fatigue on different components of functional impairments in daily life in patients with a neuromuscular disorder.

In this article we will answer the following research questions. 1) How many patients with these neuromuscular disorders experience severe fatigue?; 2) Are there differences in fatigue severity, demographical variables and various functional impairments between the different neuromuscular disorders?; 3) What is the contribution of physical functioning, social functioning, mental health and bodily pain to fatigue severity in three different relatively common neuromuscular disorders?

METHODS

Patients

Adult patients in the age of 18 to 65 years with a definite diagnosis of a neuromuscular disorder who could be classified into one of the following three diagnostic categories were asked to participate: (1) facioscapulohumeral muscular dystrophy (FSHD), (2) adult-onset myotonic dystrophy (MD) or (3) hereditary motor and sensory neuropathy type I (HMSN). Part of the patients was recruited from our Neuromuscular Centre, Radboud University Nijmegen Medical Centre in the Netherlands. The remaining part of the patients was recruited from the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland, VSN).

In total, 900 patients were informed by a letter and received a booklet with questionnaires (described below) at home. Subjects were asked which diagnosis was made and if this was done by a neurologist or clinical geneticist.

The study used a cross-sectional design to assess fatigue in patients with a neuromuscular disorder. Written information about the purpose of the study was provided to all patients. The study was approved by the local ethics committee.

Fatigue severity

The Checklist Individual Strength (CIS*)* is a 20-item questionnaire and measures the following four separate aspects of fatigue during the previous two 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 indicated high levels of fatigue, high levels of concentration problems, low motivation and low levels of activity (22). The CIS had good internal consistency and split-half reliability (27). A CIS-fatigue score equal to or higher than 35 was used to identify severe fatigue (28).

Functional impairment in daily life

The following subscales of the Short Form-36 were used to assess different areas of functional impairments in daily life: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, mental health, bodily pain and general health perception (29). The transformed scores for all SF-36 scales ranged from 0 to 100. For each subscale a higher score indicated better functioning or less pain.

Statistics

Data analysis was performed using SPSS for Windows (version 11.0). Descriptive statistics were used to describe the sample. Normality was tested according to the Kolmogorov-Smirnov test. t-tests, chi-square and one-way ANOVA's were performed to test differences between groups. In case of an overall significance, the Bonferonni correction was applied to compare the three patient groups. P values <= 0.05 were regarded as statistically significant. Correlations were calculated with the Pearson coefficient (r). In order to examine the contribution of physical functioning, social functioning, mental health and bodily pain in relation to fatigue severity, linear regression analyses (enter-method) were performed.

RESULTS

From the 647 adult patients who returned the questionnaires (72%), 49 patients were excluded. Excluded were patients without a diagnosis of FSHD, MD or HMSN type I (n=30), and incomplete booklets (n=19). A total of 598 patients fitted the inclusion criteria and completed the questionnaires (66%). This group consisted of 139 FSHD patients, 322 MD patients, and 137 HMSN-I patients. Diagnoses of a quarter of these patients were made at our hospital according to established criteria (30). Results from this sub-group did not differ from the results of the total group of participants. Demographic characteristics of the complete groups are listed in Table 3.1. No significant differences were found in age, gender and marital status between the three groups. The MD group had a significantly lower level of education than the two other patient groups.

TABLE 3.1. Demographic characteristics of patient groups

	FSHD N=139 Mean (SD)	**MD** N=322 Mean (SD)	**HMSN** N=137 Mean (SD)
Mean age	43.7 (10.1)	43 (10)	42.5 (10.7)
Age range	22–61	18–63	19-63
Gender (M/F)	49%/ 51%	47%/ 53%	41%/ 59%
Marital status (%)			
married/living together	74%	70%	69%
single	25%	30%	31%
missing information	1%	---	---
Education level (%)*			
lower	32%	53%	28%
intermediate	34%	28%	27%
upper	34%	19%	29%
missing information	1%	---	---

* significantly different between MD and FSHD and between MD and HMSN (p-value < 0.05)

Fatigue and functional impairments in FSHD, MD and HMSN

All patient groups experienced high levels of fatigue. The mean CIS-fatigue score in the FSHD group was 36.5 (SD 12.5), in the MD group 40.4 (SD 11.8) and in the HMSN group 37.4 (SD 12.2). In the FSHD group 61% was severely fatigued, in the MD group 74% and in the HMSN group 64%.

In Table 3.2, a comparison is made between the three patient groups (FSHD, MD, HMSN), with regard to functional impairments in daily life. The MD group reported having significantly more concentration problems, higher levels of reduced motivation and reduced levels of activity. The MD group perceived lower general health but experienced less bodily pain than the FSHD and HMSN patients.

TABLE 3.2. Patient groups and their mean values on the main outcome measures

	FSHD N=139 Mean (SD)	**MD** N=322 Mean (SD)	**HMSN** N=137 Mean (SD)	p-value
CIS				
CIS-fatigue	36.5 (12.5)[b]	40.4 (11.8)[ac]	37.4 (12.2)[b]	0.002
CIS-concentration	12.3 (8.2)[b]	16.8 (8.3)[ac]	13.8 (8.7)[b]	0.000
CIS-motivation	12 (5.9)[b]	16.8 (6.6)[ac]	12.2 (6.1)[b]	0.000
CIS-activity	10.1 (5.5)[b]	13.2 (5.6)[ac]	9.4 (5.5)[b]	0.000
SF-36				
physical functioning	45.2 (31.4)	48.4 (28.2)	53.1 (26.4)	ns
social functioning	71.6 (24.2)	69.9 (24.3)	67.5 (24.3)	ns
role limitations physical	47.9 (42)	48.2 (39.7)	48.9 (39)	ns
role limitations emotional	69.5 (41.6)	73.9 (37.6)	67.4 (41.6)	ns
mental health	72.6 (17)	72.7 (18)	68.9 (19.2)	ns
bodily pain	66.6 (23.8)[b]	75.4 (25.3)[ac]	68.5 (25.5)[b]	0.001
general health perception	51.7 (21.6)[b]	40.5 (22.3)[ac]	52.5 (20.7)[b]	0.000

A higher value indicates more complaints or impairments

[a] Significantly different from FSHD, Bonferonni $p<0.05$

[b] Significantly different from MD, Bonferonni $p<0.05$

[c] Significantly different from HMSN, Bonferonni $p<0.05$

Age related problems

In the FSHD group and the MD group, age correlated significantly with fatigue severity (FSHD: $r=0.19$, $p=0.002$; MD: $r=0.17$, $p=0.002$). In all three patient groups, higher age is associated with more impairments in physical functioning and more bodily pain. Among the MD patients, age correlated significantly with all subscales of the SF-36 and with reduced motivation and reduced activity of the CIS.

Severely fatigued patients

Severely fatigued patients (CIS-fatigue >= 35) were compared with less fatigued patients (CIS-fatigue < 35) within the three neuromuscular disorders. Severely fatigued FSHD patients, MD patients and HMSN patients had significantly more concentration problems, higher scores on

reduced motivation and reduced levels of physical activity. Severely fatigued neuromuscular patients also had significantly lower scores at all subscales of the SF-36.

Contribution of different dimensions to fatigue severity

Regression analyses have been performed to examine the contribution of different dimensions in relation to fatigue severity (Table 3.3). For each group separate analyses were carried out, with CIS-fatigue as the dependent variable. In none of the groups did age contribute to fatigue severity. In the FSHD group, physical functioning, social functioning and bodily pain contributed significantly to fatigue severity. In the MD group physical functioning and social functioning contributed significantly to fatigue severity. In the HMSN group none of the independent variables contributed significantly to fatigue severity. The correlations between CIS-fatigue and the SF-36 sub-scales are weaker in the HMSN group than in the FSHD and MD group.

TABLE 3.3. Linear regression analysis to predict fatigue severity

	Dependent variable CIS-fatigue severity					
	FSHD Beta	**FSHD** P	**MD** Beta	**MD** p	**HMSN** Beta	**HMSN** p
Independent variables						
physical functioning	-.228	0.010	-.398	0.000	-.188	0.056
social functioning	-.219	0.038	-.157	0.015	-.107	0.358
mental health	-.031	0.725	-.112	0.048	-.166	0.121
bodily pain	-.195	0.042	-.062	0.284	-.146	0.121
age	.022	0.900	-.087	0.114	-.148	0.083
Total R^2 (adjusted)	.238		.270		.143	

DISCUSSION

This is the first cross-sectional study in which experienced fatigue has been investigated in three large homogeneous groups of neuromuscular disorders with validated measurements, as far as we know. This study demonstrated that in the investigated patient groups of FSHD, MD and HMSN-I 61-74% were severely fatigued. This finding means that the experience of severe fatigue is a major complaint in most patients with these neuromuscular disorders. In all three patient groups, being severely fatigued was associated with higher levels of functional impairments in daily life.

Further, results showed that patients with MD have significantly higher scores of severe fatigue, reported significantly more problems with concentration (CIS-concentration), and have significantly more difficulties with initiating and planning (CIS-reduced motivation) than the other two patient groups. Daytime sleepiness is an established clinical manifestation of MD (18,31-32). It is possible that MD patients confuse the experience of fatigue with daytime sleepiness, which may have affected the CIS-fatigue scores of the MD patient group. However, van der Werf et al showed that experienced fatigue, measured with the CIS-fatigue, and daytime sleepiness are different clinical manifestations in MD (33).

In addition, we found that MD patients have a significantly lower education level than the FSHD and HMSN patients. These differences could be explained by disease-specific problems associated with a multisystem disorder like MD. Mental dysfunction in MD, such as reduced intelligence, lower levels of concentration and initiation have been recognised, in contrast to the lack of such defects in other disabling neuromuscular disorders (18, 31). FSHD patients and HMSN patients turned out to have higher scores of bodily pain than the MD patients. These results are consistent with reports of presence of pain in other studies in FSHD and HMSN patients (14-16). Pain, particularly back pain, is often cited as a problem but is poorly studied in MD patients (31).

In all groups age and fatigue severity do not seem related, as no contribution of age and fatigue severity was found in the regression analyses. Karlsen showed that fatigue severity is not regarded as part of the normal aging process (5).

Significant correlations between age and functional impairments in daily life suggest that higher age is associated with more impairments in physical functioning and bodily pain in all three patient groups. This result is in accordance with the fact that these disorders are progressive. Literature already described an increase of physical limitations with age (17-19). In MD, age also correlated with all other functional impairments. These results were in line with the differences between the three neuromuscular disorders (18,31).

Compared with healthy controls, mentioned in the manual of the Dutch version of the SF-36, the mean scores of all three neuromuscular patient groups were lower on all SF-36 subscales (26). In addition, the severely fatigued patients in all three neuromuscular disorders scored lower than the non-severely fatigued patients, suggesting a relation between fatigue and functional impairments. Herlofson et al showed that fatigued patients with Parkinson's disease reported more problems in areas of functional limitations and the patients with fatigue had a more advanced disease than those without fatigue, measured by a disease severity scale for Parkinson's disease (11). A study of Fisk et al found that fatigue has a significant effect on the general health status in patients with multiple sclerosis (12). They found that disease classification and neurological impairment had little bearing on fatigue in patients with multiple sclerosis. In our study we have not used a disease severity scale, so we can not investigate the relation between fatigue severity and disease severity in these disorders.

Regression analyses suggest that in FSHD patients physical functioning, bodily pain and social functioning are related to fatigue severity. In MD patients only physical functioning and social functioning were related to fatigue severity. In HMSN patients none of the dimensions contributed independently to fatigue severity. Thus, in this group fatigue is less clearly related to functional impairments. Possibly, factors that we did not measure, play a more prominent role in the contribution of fatigue.

The impact of fatigue in health related quality of life in patients with neuromuscular disorders has not been studied so far.

Our findings must, however, be interpreted in the context of methodological limitations. Firstly, the cross-sectional design of this study makes it impossible to draw conclusions on the direction of the association. Secondly, not all diagnoses were made at our hospital. About a quarter of the patients in this study come from our hospital and the diagnoses of those patients were checked.

Nevertheless, this group of patients did not differ in all main outcome variables from the remaining patients recruited from the Dutch Neuromuscular Diseases Association.
In conclusion, the present study shows that the majority of a large sample of patients with relatively common types of neuromuscular disorders experienced severe fatigue. Which factors are related to fatigue severity, appears to be different in the three neuromuscular disorders. Severe fatigue is associated with serious impairments in daily life. Therefore, experienced fatigue is a clinically and socially relevant problem in patients with a neuromuscular disorder.

REFERENCES

1. Krupp LB, Fatigue. Philadelphia: Butterworth Heinemann 2003.
2. Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis:Current understanding and future directions. J Rehabil Res Dev 2002; 39: 211-224.
3. Ford H, Trigwell P, Johnson M. The nature of fatigue in Multiple Sclerosis. J Psychosom Res 1998; 45: 33-38.
4. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology 1993;43:2016-2018.
5. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. Mov Disord 1999; 14: 237-241.
6. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord 2001; 16: 190-196.
7. Van der Werf SP, van den Broek HL, Anten HW, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur Neurology 2001; 45: 28-33.
8. Paul RH, Cohen RA Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
9. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
10. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune-mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
11. Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand 2003; 107: 1-6
12. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994; 21: 9-14
13. Werf SP van der. Determinants and consequences of experienced fatigue in chronic fatigue syndrome and neurological conditions [dissertation]. Nijmegen: University Nijmegen; 2003.
14. Teunissen LL, Eurelings M, Notermans NC, Hop JW, van Gijn J. Quality of life in patients with axonal polyneuropathy. J Neurol 2000; 247: 195-199.
15. Pfeiffer G, Wicklein EM, Ratusinski T, Schmitt L, Kunze K. Disability and quality of life in Charcot-Marie-Tooth disease type I. J Neurol Neurosurg Psychiatry 2001; 70: 548-550.
16. Piccininni M, Falsini C, Pizzi A. Quality of life in hereditary neuromuscular diseases. Acta Neurol Scand 2004; 109: 113-119.
17. Padberg GW, Lunt PW, Koch MC, Fardeau M. Diagnostic criteria for facioscapulohumeral muscular dystrophy. Neuromusc Disord 1991; 1(4): 231-234.
18. Harper PS. Myotonic dystrophy, 3rd version. London: Harcourt Publishers Ltd, 2001.

19. Gabreels-Festen AA, Bolhuis PA, Hoogendijk JE, Valentijn LJ, Eshuis EJ, Gabreels FJ.Charcot-Marie-Tooth disease type 1A: morphological phenotype of the 17p duplication versus PMP22 point mutations. Acta Neuropathol (Berl) 1995; 90(6): 645-649.
20. Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 1980; 103: 259-280.
21. Harding AE. From the syndrome Charcot, Marie and Tooth to disorders of peripheral myelin proteins. Brain 1995; 118: 809-818.
22. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
23. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
24. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients : a cross-sectional study. Ann of Oncol 2002 ; 13: 589-598.
25. Vries M de, Soetekouw PM, Meer van der JW, Bleijenberg G. Fatigue in Cambodia veterans. QJM 2000; 93: 283-289.
26. Van der Zee K, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36: Een handleiding. [SF-36, Manual Dutch version]. Noorderlijk Centrum voor Gezondheidsvraag-stukken: Groningen, 1993.
27. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue, a practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 157-170.
28. Vercoulen JH, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS). [The Checklist Individual Strength]. Gedragstherapie 1999; 32: 131-136.
29. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. Med Care 1992; 30: 473-483.
30. Emery AEH. Diagnostic criteria for neuromuscular disorders, 2nd edition. London: Royal Society of Medicine Press, 1997.
31. Harper PS, van Engelen BGM, Eymard B, Wilcox DE. Myotonic dystrophy: present management, future therapy. New York: Oxford University Press, 2004.
32. Rubinsztein JS, Rubinsztein DC, Goodhurn S, Holland AJ. Apathy and hypersomnia are common features of myotonic dystrophy. J Neurol Neurosurg Psychiatry 1998; 64: 510-515.
33. Werf van der S, Kalkman J, Bleijenberg G, van Engelen B, Schillings M, Zwarts M. The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult onset myotonic dystrophy. J Neurol Neurosurg Psychiatry 2003; 74: 138-139.

CHAPTER 4

Psychiatric disorders appear equally in patients with myotonic dystrophy, facioscapulohumeral dystrophy, and Hereditary Motor and Sensory Neuropathy type I

This chapter is accepted for publication as:
Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Psychiatric disorders appear equally in patients with myotonic dystrophy, facioscapulohumeral dystrophy, and HMSN-I. *Acata Neurol Scand, accepted.*

ABSTRACT

Objectives

To study the presence of psychiatric comorbidity assessed by the use of a structured clinical interview and self-reported questionnaires in a large sample of patients with adult-onset DM, FSHD, and HMSN-I, and to assess whether psychiatric comorbidity is related to fatigue severity and/or muscle strength.

Methods

In a cohort of 217 patients with a neuromuscular disorder (79 DM, 65 FSHD and 73 HMSN-I patients) overall psychiatric comorbidity was studied cross-sectionally with the structured clinical interview (SCID) for DSM-IV axis I disorders. Self-reported psychopathology, fatigue severity and muscle strength were assessed with the Beck Depression Inventory, SCL-90, General Health Questionnaire-12, Checklist Individual Strength, and muscle strength (MRC-scale).

Results

In all three neuromuscular disorders (DM, FSHD and HMSN), 10 to 12% of the patients met DSM IV clinical criteria for current psychiatric disorders. Lifetime psychiatric disorders were found in 32% of patients in all three patient groups. The most common psychiatric disorders were depression and phobias. A comparison of patients with and without current psychiatric disorder showed that fatigue severity and muscle strength (MRC) were not related to psychiatric comorbidity.

Conclusion

Psychiatric disorders appear equally in patients with DM, FSHD and HMSN-I and are not related to fatigue or muscle strength in these patients.

INTRODUCTION

Previous studies have documented the presence of psychiatric comorbidity in neurological disorders. These studies found high prevalence of depression (40%) in neurological patients (1,2). Similar findings have been described for depressive disorders comorbidity with specific neurological disorders such as Parkinson's disease, stroke and multiple sclerosis (3-7). Carson et al conclude that patients with various neurological diseases are at risk for developing depressive disorders (1). It has been recognised that mood disorders and anxiety disorders contribute to well being and improvement in patient's disability (8).

Only few studies have examined levels of depression and anxiety in patients with various neuromuscular disorders. The largest study of patients with various neuromuscular disorders examined psychopathology of 36 DM patients and 13 HMSN patients (9). Current diagnosis of major depression was found in 6% of patients with DM and in none of the HMSN patients. Half of the DM patients and one third of HMSN patients met the diagnosis for lifetime history of major depression. Substance related disorders has not been studied systematically in patients with neuromuscular disorders.

Fatigue is a common complaint of patients with neurological disorders, including neuromuscular disorders (3,10). An association between fatigue and psychiatric disorders has been reported in a number of neurological disorders, including Parkinson's disease and multiple sclerosis (6,8). Fatigue is a major component of a number of affective disorders, including major depression and dysthymia. We have found no studies examining the association of psychiatric disorders and fatigue in neuromuscular disorders.

The present study concerns three genetically well-defined and homogeneous populations of patients with relatively common neuromuscular disorders, namely adult-onset myotonic dystrophy (DM), facioscapulohumeral muscular dystrophy (FSHD), and hereditary motor and sensory neuropathy type I (HMSN). DM is the most common form of muscular dystrophy and is an autosomal dominantly inherited multisystemic disease characterized by myotonia, muscular weakness, cardiac abnormalities, cataract, and disorders of other systems such as the endocrine system, gastrointestinal tract , and the central nervous system, the known abnormalities of which concern cognitive processes, and affective status (11). FSHD is an autosomal dominantly inherited myopathy (12). HMSN type I is the most common genetic disorder affecting the peripheral nervous system (13-15). Thus, this study compares psychiatric comorbidity in three different neuromuscular patient populations, including a multisystem disorder, a myopathy and a neuropathy. To date, no study has compared psychiatric comorbidity in large groups of patients with DM, FSHD and HMSN using a standardized psychiatric interview and self-report questionnaires.

The aims of this study were to determine the presence of psychiatric disorders, specifically mood disorders, anxiety disorders and substance related disorders, (lifetime and current) in patients with DM, FSHD and HMSN patients, and to assess if psychiatric comorbidity was related to fatigue severity and/or muscle strength.

METHODS

Patients

Adult patients in the age of 18 to 60 years with a definite diagnosis of a neuromuscular disorder who could be classified into one of the following three diagnostic categories were asked to participate: (1) adult-onset myotonic dystrophy (DM), (2) facioscapulohumeral muscular dystrophy (FSHD) or (3) hereditary motor and sensory neuropathy type I (HMSN). Patients were recruited from the outpatient clinic of the Neuromuscular Centre of the Radboud University Nijmegen Medical Centre and the database of the Dutch Neuromuscular Diseases Association. Patients are a subgroup of patients described earlier (10).

Only ambulatory patients were included. From the 527 patients that were eligible 331 patients were willing to participate in the research project. We invited 240 patients (for each neuromuscular disorder at least 70 patients) and 217 patients (79 DM, 65 FSHD and 73 HMSN patients) complete data could be collected. Patients dropped out (n=23) for several reasons: high travel distance, inability to take a day off or personal reasons. Written informed consent was obtained from all participating patients. The following demographic features were collected: age, gender, marital status, and highest level of education and current status of employment. The Committee on Research Involving Human Subjects approved the study.

Psychiatric comorbidity based on a structured clinical interview

Psychiatric disorders were valuated using the Structured Clinical Interview for DSM-IV (SCID-I-R) axis 1 disorders (16). The Dutch translation of the SCID was used, by which post-interview diagnoses based on DSM-IV criteria can be generated (17). Three broad categories of psychiatric disorders were assessed: mood disorders (depression and dysthymic disorder), anxiety disorders (panic disorder, simple phobia, PTSD, general anxiety disorder and obsessive compulsive disorder), and substance related disorders (alcohol and drugs abuse). According to DSM IV guidelines a distinction was made between current (disease manifest in the past 30 days) and lifetime (disease not manifest in the past 30 days) diagnoses.

Psychiatric comorbidity based on self-reported questionnaires

The Beck Depression Inventory (BDI) is a 21-item standardised self-report questionnaire measuring depression on a 4-point scale ranging from 0 to 3 (18).

The Symptom Checklist-90 (SCL-90) measures self-reported psychopathology. This questionnaire asks for anxiety, agoraphobia, depression, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity, hostility and sleep disturbances (e.g., light and fragmented sleep, difficulties with sleep initiating) (19). The total score can be considered as a general measure of psychological distress.

The 12-item version of the General Health Questionnaire (GHQ-12) was used as a screening tool for psychiatric disorders within the general population (20). Higher scores indicate increasing levels of psychiatric morbidity.

Fatigue severity
The Checklist Individual Strength (CIS) is a 20-item questionnaire and measures the following four aspects of fatigue during the previous two 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 high levels of fatigue, high levels of concentration problems, low motivation and low levels of activity (21,22). The CIS questionnaire has good reliability and validity, including discriminative validity (22,23). A CIS-fatigue score of 35 or more was used to identify severe fatigue (21).

Muscle strength
Muscle strength was determined using the Medical Research Council (MRC) grading scale (MRC; 0 to 5) investigating the strength of the shoulder abductors, grip force, foot extensors and knee extensors (24). These eight values (both left and right) were averaged.

Statistics
Data analysis was performed using SPSS for Windows (version 11.0). Descriptive statistics were used to describe the sample. Chi-square, t-test and one-way ANOVAs were performed to test differences between groups. In case of an overall significance, the Bonferroni correction was applied to test differences between groups. For comparison between patients with and without psychiatric disorder the Mann-Whitney test was used. Significance level was set at $p < 0.05$ (two-tailed). Correlations were calculated with the Spearman coefficient (r) correlation.

RESULTS

The patient sample consisted of 79 DM patients, 65 FSHD patients, and 73 HMSN patients. Neuromuscular diagnoses of the patients were verified according to established criteria (25). In order to verify the diagnoses, the patients neurologist were contacted. The diagnoses of all patients were genetically confirmed in the patient, or in a first degree family member.
Demographic characteristics of the groups are summarized in Table 1. No significant differences were found in age, gender, marital status, level of education, and employment between the three groups. The patients who refused to take part in the study did not differ from the participating subjects with regard to age, gender, marital status, level of education, employment status, fatigue severity and GHQ-12 score in each neuromuscular disorder.

Psychiatric comorbidity
We found no significant differences in current and lifetime psychiatric comorbidity between the three neuromuscular disorders. The presence of at least one lifetime psychiatric disorder was found in 33% of the DM patients, 31% of the FSHD patients and in 34% of the HMSN patients (Table 4.2). A current psychiatric disorder (1-month) was reported in 11% of the DM patients, 12% of the FSHD patients and in 11% of the HMSN patients. The most common psychiatric disorders were depression and phobias.

TABLE 4.1. Demographic characteristics of the three neuromuscular patient groups

	DM N=79 mean (sd)	**FSHD** N=65 mean (sd)	**HMSN-I** N=73 mean (sd)
Mean age	41 (9.9)	43.1 (10.3)	42.4 (9.8)
Age range	22-56	22-60	20-58
Gender (male/female)	56% / 44%	59% / 41%	41% / 59%
Marital status			
married/living together	53 (67%)	52 (80%)	49 (68%)
divorced	4 (5%)	3 (5%)	4 (5%)
widowed	---	2 (3%)	4 (5%)
living independently	13 (17%)	6 (9%)	11 (15%)
living with parents	9 (11%)	2 (3%)	5 (7%)
Higher education (>= 12 years)	17 (21%)	18 (28%)	20 (27%)
Employment			
work outside home	50 (63%)	41 (63%)	45 (62%)
household	10 (13%)	7 (11%)	3 (4%)
study/school	2 (3%)	---	8 (11%)
disablement insurance act	17 (22%)	20 (31%)	19 (26%)
partial disablement insurance act	16 (20%)	6 (9%)	9 (12%)
sick leave	3 (4%)	3 (6%)	5 (7%)

TABLE 4.2. Proportions of lifetime and 1-month prevalence of DSM-IV diagnoses in the three neuromuscular patient groups (DM, FSHD and HMSN)

	DM N=79		**FSHD** N=65		**HMSN** N=73	
	Lifetime %	1-month %	Lifetime %	1-month %	Lifetime %	1-month %
Mood disorders	19	2.5	16.9	4.6	19.2	2.7
depression	15.2	2.5	13.8	3.1	16.4	2.7
dysthymic	3.8	---	3.1	1.5	2.7	---
Anxiety disorders	17.7	7.6	15.4	6.1	19.2	5.5
panic disorder	---	---	1.5	---	2.7	---
simple phobia	12.7	3.8	10.8	3.1	12.3	2.7
PTSD	---	---	---	---	2.7	---
gen. anxiety disorder	2.5	2.5	3.1	1.5	1.4	1.4
obs. comp. disorder	2.5	1.3	---	---	---	1.4
Alcohol abuse	1.3	1.3	1.5	---	1.4	---
Drugs abuse	2.5	1.3	---	---	---	---
One or more DSM-IV diagnoses	32.9	10.7	30.8	12.3	34.2	10.6

No significant differences were found between the three groups on self-reported psychopathology (Table 4.3), fatigue severity and muscle strength. However, DM patients reported to have significantly higher scores on concentration problems and reduced motivation, while HMSN patients reported significantly more sleep problems (Table 4.3). DM patients had significantly higher score on reduced activity than HMSN patients (Table 4.3).

Current psychiatric comorbidity in relation to fatigue severity and muscle strength
Comparisons have been made between patients with and without current psychiatric disorder in each neuromuscular disorder (DM, FSHD and HMSN). No significant differences were found in age, gender, fatigue severity and muscle strength (MRC).

Lifetime psychiatric comorbidity in relation to fatigue severity and disease severity
No significant differences were found in age, gender, fatigue severity and muscle strength between patients with and without a lifetime psychiatric disorder in each neuromuscular disorder.

TABLE 4.3. Complaints and symptom characteristics of the three neuromuscular patient groups

	DM N=79 mean (sd)	**FSHD** N=65 mean (sd)	**HMSN-I** N=73 mean (sd)	p-value
BDI-total	6.2 (4.7)	5.3 (5.8)	6.1 (6.6)	ns
SCL-90				
anxiety	12.0 (3.9)	12.3 (4.4)	13.5 (5.3)	ns
agoraphobia	7.7 (1.4)	8.3 (3.4)	7.8 (2.0)	ns
depression	21.6 (5.3)	21.4 (8.5)	23.1 (9.8)	ns
somatisation	18.9 (5.1)	19.0 (6.6)	20.4 (6.2)	ns
obsessive-compulsive behaviour	14.9 (4.7)	13.5 (6.2)	13.9 (5.0)	ns
interpersonal sensitivity	24.3 (6.8)	23.3 (8.7)	24.6 (8.7)	ns
hostility	6.9 (1.6)	7.0 (2.0)	7.2 (2.1)	ns
sleep	4.0 (1.6)[c]	4.4 (2.1)[c]	5.3 (2.4)[ab]	0.001
total	121.7 (27.2)	120.1 (41.0)	126.9 (37.5)	ns
GHQ-12 total	1.9 (2.6)	2.4 (3.2)	2.6 (3.8)	ns
CIS				
fatigue severity	32.1 (11.7)	34.1 (10.5)	34.9 (12.9)	ns
concentration problems	16.3 (7,3)[bc]	12.0 (7.4)[a]	13.1 (8.7)[a]	0.003
reduced motivation	14.0 (5.7)[bc]	10.6 (4.9)[a]	10.7 (5.0)[a]	0.000
reduced activity	10.7 (4.8)[c]	8.9 (5.1)	8.3 (4.9)[a]	0.01
Muscle strength (MRC)	3.6 (0.9)	3.7 (0.9)	3.7 (0.9)	ns

A higher value indicates more complaints or symptoms
[a] Significantly different from DM, Bonferonni $p<0.05$
[b] Significantly different from FSHD, Bonferonni $p<0.05$
[c] Significantly different from HMSN, Bonferonni $p<0.05$

DISCUSSION

In this prospective study, lifetime and current psychiatric disorders (mood disorders, anxiety disorders and substance related disorders) were equally prevalent in a large cohort of DM, FSHD and HMSN-I patients. Approximately 11% of the 217 patients we studied had a current psychiatric disorder and 32% had lifetime psychiatric comorbidity. The most common psychiatric disorders were depression and phobias. Psychiatric comorbidity was not associated with fatigue severity or muscle strength in the various neuromuscular disorders.

These results concur with those of Phillips et al. who found that DM patients had higher depression scores than HMSN patients or healthy controls (26). This difference may in part be explained by the smaller sample size of DM patients in their study and differences in the study methodology (self-report versus structured interview). However, Bungener et al. showed that DM patients did not present significant depressive disorders according to DSM-III-R criteria in comparison with FSHD patients, although DM patients did present symptoms of mild depression (27). Furthermore, they found that FSHD patients presented significantly greater symptoms of depression and anxiety than control subjects (27). In a study of Meola et al. none of the DM patients fulfilled DSM IV criteria for axis I and II disorders (28). However, Winblad et a. indicates deviant personality in classical DM-1 in comparison to healthy controls and to patients with other muscle disorders with known brain disorder (29).

Bungener et al showed that DM patients have more emotional disorders than FSHD patients and healthy controls (27). These disorders are manifestated as anhedonia and lack of expressiveness as evidenced by monotonous mood, apathy, and inability to anticipate pleasure. Other studies found a range of mental disturbances in patients with DM: moodiness, apathy, excessive somnolence, lack of motivation and diminished mental capacity (11,33). Myotonic dystrophy is a multi-system disorder, including the brain. Although neuropathological and neuroradiological abnormalities have been reported in the literature, we found only few studies that investigated neuropathological and neuroradiological abnormalities and cognitive impairment, (30-32). However, in our study we investigated the presence of psychiatric morbidity and not cognitive impairment.

We found a higher score on reduced motivation in patients with myotonic dystrophy than in patients with FSHD and HMSN. However, we found no more psychiatric disorders in DM patients than in the other two groups. In addition, most patients with myotonic dystrophy did not have clinical depression when interviewed and therefore the higher reduced motivation in these patients cannot be explained in these terms. It is possible that features like ptosis, myopathic faces and dysarthric speech noted in DM can give a false impression of affective state.

Comparing our data with the general population, as many as 41% of the Dutch adult population under 65 year reported having experienced one or more psychiatric disorders at some time in their lives (34). Among them were 19% who had experienced a mood disorder and 19.3% an anxiety disorder. The 1-month rates were 3.9% for mood disorders and 9.7% for anxiety disorders. So, the presence of psychiatric comorbidity in patients with a neuromuscular disorder seems to be similar to the prevalence of psychiatric morbidity in the general Dutch population. The most common psychiatric disorders were depression and phobias. Fear of heights was the most represented type of single phobia, followed by those of animals and insects, closed spaces, and blood. There was no difference in type of simple phobia between the three neuromuscular disorders. We do not find studies demonstrating an association between neuromuscular disorders and simple phobia.

Our study might have the following methodological limitations. Firstly, a selection bias is possible, because we only investigated ambulant patients. However, we have GHQ scores from 381 non-participating patients with neuromuscular disorders (243 DM, 74 FSHD and 64 HMSN patients), an instrument that has been validated as a screening tool for psychiatric disorder. We found that the investigated groups did not differ in GHQ-12 scores from the not included

patients in this study. So it is unlikely that there is a systematic bias in our sample. Secondly, the investigators seeing the patients were not blinded to their diagnosis. This is not an easy problem to overcome, as many patients with DM have characteristics faces. Thirdly, a well known methodological problem in studying psychiatric comorbidity in the context of chronic diseases is that symptoms of somatic illness, for instance reduced appetite, lack of energy, weight changes, and insomnia, partly overlap with symptoms of psychiatric disorders, thus creating diagnostic difficulties. However, this problem is less serious in neuromuscular disorders, as the symptoms of the majority of neuromuscular disorders do not overlap with somatic disturbances that may be found in psychiatric disorders. Finally, in the absence of validated objective disease severity scales in neuromuscular disorders is a methodological problem in studying disease severity in various neuromuscular disorders.

In conclusion, the present study shows that psychiatric comorbidity occurs equally in patients with DM, FSHD and HMSN. Current and lifetime psychiatric comorbidity is not associated with experienced fatigue and/or muscle strength.

REFERENCES

1. Carson AJ, Postma K, Stone J, Warlow C, Sharpe M. The outcome of depressive disorders in neurology patients: a prospective cohort study. J Neurol Neurosurg Psychiatry 2003; 74: 893-896.
2. Williams LS, Jones WJ, Shen J, Robinson RL, Weinberger M, Kroenke K. Prevalence and impact of depression and pain in neurology outpatients. J Neurol Neurosurg Psychiatry 2003; 74: 1587-1589.
3. Krupp LB. Fatigue. Philadelphia: Butterworth Heinemann, 2003.
4. Lobentanz IS, Asenbaum S, Vass K, Sauetr C, Klösch G, Kolleger H, Kristoferitsch W, Zeitlhofer J. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand 2004; 110: 6-13.
5. Rojo A, Aguilar M, Garolera MT, Cubo E, Navas I, Quintana S. Depression in Parkinsons' disease: clinical correlates and outcome. Parkinsonism Related Disord 2003; 10: 23-28.
6. Schrag A. Psychiatric aspects of Parkinson's disease, an update. J Neurol 2004; 51: 795-804.
7. Werf van der S, van der Broek H, Anten H, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur J Neurol 2001; 45(1): 28-33.
8. Surtees PG, Wainwright NWJ, Khaw KT, Day NE. Functional health status, chronic medical conditions and disorders of mood. Br J Psychiatry 2003; 183: 299-303.
9. Rubinsztein JS, Rubinsztein DC, Goodburn S, Holland AJ. Apathy and hyprsomnia are common features of myotonic dystrophy. J Neurol Neurosurg Psychiatry 1998; 64: 510-515.
10. Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I patients. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.
11. Harper PS. Myotonic dystrophy, 3rd version. London:Harcourt Publishers Ltd, 2001.
12. Engel AG, Franzini-ArmstrongC. Myology, 3rd edition. New York: McGraw-Hill, 2004.
13. Dyck PJ, Thomas PK. Peripheral neuropathym 4th edition. London: Saunders, 2005.

14. Harding AE, Thomas PK .The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 1980; 103: 259-80.
15. Harding AE. From the syndrome Charcot, Marie and Tooth to disorders of peripheral myelin proteins. Brain 1995; 118: 809-818.
16. First M, Spitzer R, Gibbon M, Williams J. Structured clinical interview for DSM-IV axis 1 disorders. Washington DC: American Psychiatric Press, 1997.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed.). APA Washington DC, 1994.
18. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
19. Koeter MW, Ormel J.General Health Questionnaire, Handleiding Nederlandse bewerking (General Health Questionnaire, Manual Dutch version). Lisse: Swets & Zeitlinger Lisse, 1991.
20. Goldberg DP, Williams P. A User's Guide to the General Health Questionnaire. NFER-Nelson Windsor, 1988.
21. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
22. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
23. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 157-170.
24. Medical Research Counsil. Aids to the examination of the peripheral nerve injuries. Her Majesty's Stationery Office London, 1981.
25. Emery AEH. Diagnostic criteria for neuromuscular disorders, 2nd edition Royal Society of Medicine Press London, 1997.
26. Phillips MF, Steer HM, Soldan JR, Wiles CM, Harper PS. Daytime somnolence in myotonic dystrophy. J Neurol 1999; 246: 275-282.
27. Bungener C, Jouvent R, Dalaporte C. Psychopathological and emotional deficits in myotonic dystrophy. J Neurol Neurosurg Psychiatry 1998; 65: 353-356.
28. Meola G, Snasone V, Perani D et al. Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2). Neuromuscul Disord 2003; 13: 813-821.
29. Winblad S, Lindberg C, Hansen S. Temperament and character in patients with classical myotonic dystrophy type 1 (DM-1). Neurmusc disord 2005; 15: 287-292.
30. Oyamad R, Hayashi M, Katoh Y, Tsuchiya K, Mizutani T, Tominaga I, Kashima H. Neurofibrillary tangles and deposition of oxidative products in the brain in cases of myotonic dystrophy. Neuropathology 2006; 26: 107-114.
31. Ogata A, Terae S, Fujita M, Tashiro K. Anterior temporal white matter lesions in myotonic dystrophy with intellectual impairment: an MRI and neuropathological study. Neuroradiology 1998; 40: 411-415.
32. Miaux Y, Chiras J, Eymard B, Lauriot MC, Radvanyi H, Martin N, Delaporte C. Cranial MRI findings in myotonic dystrophy. Neuroradiology 1997; 39: 166-170.
33. Harper PS, van Engelen BGM, Eymard B, Wilcox DE. Myotonic dystrophy : present management, future therapy. New York: Oxford University Press, 2004.
34. Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998; 33: 587-595.

CHAPTER 5

Ambulatory disabilities and the use of walking aids in HMSN I patients

This chapter is accepted for publication as:
Van der Linden MH, Kalkman JS, Hendricks HT, Schillings ML, Zwarts MJ, Bleijenberg G, van Engelen BGM. Ambulatory Disabilities and the Use of Walking Aids in HMSN I patients. *Disability and Rehabilitation, accepted.*

ABSTRACT

Objectives

To determine the level of ambulatory disability in well ambulant patients with Hereditary Motor and Sensory Neuropathy type I (HMSN I), and to identify the related demographic, physical and psychological variables.

Methods

Seventy-five ambulatory HMSN I patients, aged 20 to 58 years, were measured in a cross-sectional assessment, addressing demographics, disability of ambulation and mobility (Sickness Impact Profile), muscle strength (Medical Research Council (MRC)), use of walking aids, physical activity (actometer), fatigue (Checklist Individual Strength), and quality of life (EuroQoL).

Results

Seventy-two percent of the patients perceived significant amount of ambulatory disability. These patients were less active, and more fatigued compared to patients without ambulatory disability, and healthy reference groups. The total patient sample showed distal paresis (mean MRC = 3.3), a high level of pain- discomfort (76%), but normal levels of employment (62.7%) and anxiety-depression (20%). Walking aids were used by 49% of the patients. These patients were older, less active, more fatigued, had less muscle strength, and perceived more disabilities of ambulation, and mobility than non-users. Of the patients without walking aids, 41% perceived a significant amount of ambulatory disability.

Conclusion

Ambulatory disability frequently occurs in well ambulant HMSN I patients. The use of walking aids is not completely in accordance with the perceived ambulatory disability.

Therefore prescription requires specific attention as well as complaints about pain and fatigue.

INTRODUCTION

Hereditary motor and sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth disease (CMT), is among the most commonly inherited neuropathies, with a prevalence of 1 in 2.500 people(1). The most common form, type IA, is caused by a duplication of the peripheral myelin protein 22 gene (PMP22) on chromosome 17 (2). The duplication causes an initial hypermyelination of the distal large myelinated fibres, followed by a demyelination when the disease progresses. The clinical characteristics of HMSN I are progressive and include muscle weakness and atrophy of the distal lower leg muscles, and areflexia and sensory impairment with loss of touch, pain, vibration and joint position sense (3-7). Due to the muscular imbalance, patients develop foot deformities such clawing of the toes, hammertoes, pes cavus and ultimately per eyuinovarus(8). The patients mainly complain about spraining, stumbling, poor balance and clumsy gait, as well as difficulty with running, jumping and climbing stairs (7,8). Then neurological and orthopaedic impairments may lead to problems at the level of activities and participation.

Ambulatory disability has been addressed in HMSN I patients before: Birouk et al. and Holmberg et al. used a 4-point scale to address functional disability of ambulation and graded ambulatory problems as mild or moderate when patients were still able to walk unaided (6,9). Since HMSN I patients are usually not totally wheelchair confined, many young and middle-aged HMSN I patients who walk independently are thus regarded as non- or only mildly- disabled in the literature. This seems equivocal when looking at the patients' complaints in clinical practice. Therefore, the level of perceived ambulatory disability in HMSN I patients needs further attention.

The level of experienced ambulatory disabilities and patients' participation is likely to be determined by several demographic, physical and psychological factors (10). Not the actual physical impairments of HMSN patients, but their perceived disability appeared to affect the level of patients' participation (15). The extent to which HMSN I patients perceive themselves as ambulatory disabled, has not been studied systematically in well ambulant HMSN I patients before. Pfeiffer et al. measured experienced ambulation and mobility problems in a sample of 50 middle-aged HMSN I patients and found no significant differences compared to healthy elderly and persons with stroke (10). However, a comparison with healthy subjects of similar age was not made. Other studies did not use validated measurements for scoring disability (11) or were performed in non-homogeneous patient samples (12-14). The use of walking aids, such as insoles, orthotics, walkers and wheelchairs can alleviate patients' complaints, but has not been studied in this context as well.

Therefore, in this study the following questions will be addressed: (1) What is the level of ambulatory disability in well ambulant HMSN I patients, and (2) which demographic, physical and psychological variables differ between patients, based on the presence of ambulatory disability and the use of walking aids?

METHODS

Participants

Patients, aged 18 to 60 years, were recruited from databases of the Dutch Neuromuscular Diseases Association. A total of 220 HMSN type I patients were informed by a letter and asked to fill out and return a booklet of questionnaires. The booklets were returned by 158 patients, of which 135 met the eligibility criteria. The eligibility criteria consisted of a positive diagnosis of HMSN I, absence of other neurological or movement disorders, and the ability to walk unassisted over 10 minutes. Eighty six patients willing to take part in the study were invited to the hospital for further assessment, of which 75 completed the measurements. A total of 11 patients dropped out due to the length of travel time, the inability to take a day off, or for personal reasons.

The patients' neurologist or clinical geneticist received a letter verifying the diagnosis. The diagnosis was based on family history, electromyographic (EMG) data, and histological or DNA proof, if available. The patients that refused to take part in the study did not differ from the research subjects with regard to age, estimated maximum walking duration, use of walking aids or employment status. Written informed consent was obtained from all patients. The regional ethics committee approved the study.

Outcome variables

Information was gathered by means of a cross-sectional assessment. Demographic features were collected through a self-reported general questionnaire and included age, marital status, level of education, and current status of employment. The demographic features were compared with the population statistics available from the Central Bureau of Statistics (CBS 2002®).

Muscle strength (ankle plantar flexion, knee extension, and grip strength) was measured bilaterally on an ordinal 6-point scale (0-5) according to the Medical Research Council (MRC) (16). Mean MRC scores were calculated for the combined ankle and knee strength, and the ankle and grip strength, as HMSN preferentially affects the distal body parts.

Two subscales of the Sickness Impact Profile (SIP) addressed the perceived disability of ambulation (SIP-A) and mobility (SIP-M) (17,18). The SIP-A score (12 items) assessed the need for walking aids, personal assistance or resting while walking normally, up the stairs, or up a hill. The SIP-M score (10 items) addressed the ability to get out of the room or the house, and the ability to travel. Affirmative answers were summed up and weighted for each category. The SIP-scores were compared with the scores of a reference group of 90 healthy people, consisting of 35 men and 55 women (mean age 37.1 years, sd 10.9), who participated as controls in previous studies at the Expert Centre Chronic Fatigue. Based on the SIP-A score, the patients were divided in two groups: a group with and a group without significant ambulatory disability. The mean and two times the standard deviation of the reference population (2.3 + 2* 12.6= 27.5) was used as a cut-off point.

The subscale CIS-fatigue of the Checklist Individual Strength (CIS) was used to address the level of fatigue severity (22,23). The score on this 8-item questionnaire ranged from 8 (no fatigue at all) to 56 (maximally fatigued). Each item was scored on a 7-point Likert scale. High scores indicate high level of fatigue severity, a score of ≥ 35 indicates that a patient is severely fatigued (22).

The level of physical activity was assessed using an actometer, a device worn by the patients around the ankle for 12 consecutive days (19). The actometer measured the number of accelerations over a 5-minute period. A general physical activity score was calculated by averaging the number of accelerations over the 12-day period. The mean actometer scores were compared with the scores of a reference group consisting of 24 males and 23 females (mean age 40.1 years, range 19-63 years), who participated in previous studies at the Expert Centre Chronic Fatigue (19). Furthermore, patients were asked to estimate their maximum walking duration on a 3-point scale (< 10 min, 10 min-1 hr, >1 hr). The use of walking aids was defined as a single or multiple positive score on a list of items consisting of: electrical wheelchair, hand rim propulsed wheelchair, walker, cane, orthopaedic shoes, and other orthopaedic orthoses.

We used 3 domains of the EuroQol questionnaire to address the patients' deterioration in quality of life: self care, pain- discomfort, and anxiety- depression (20). Each of the domain was scored on a 3-point scale ranging from 1-3, increasing with the severity of the complaints. For example, the item pain- discomfort distinguished between 1) no, 2) moderate, and 3) severe pain or discomfort. The percentage of patients that reported a score of 2 or 3 was calculated for each domain. Furthermore, patients were asked to mark their current health state on a visual analogue scale (VAS) calibrated from zero ('worst imaginable health state') to 100 ('best imaginable health state'). The VAS has recently been proven to be a valid, reliable, and responsive measure of global quality of life (21).

Statistical analysis

Patients were divided in two groups based on the presence of significant ambulatory disability (SIP-A > 27.5). Patients were also stratified according to whether or not they used walking aids. A student's t-test was used to test group differences for continuous variables. Associations between dichotomous variables and walking aids were tested using the Chi-square test. Spearmann correlation coefficients were calculated to test correlations between non-parametric parameters. Linear multiple regression was used to calculate the explained variance of ambulatory disability. Statistical significance was tested at two levels, $p < 0.05$ (*) and $p < 0.01$ (**), by using SPSS software (SPSS 11.0, Inc., Chicago, IL).

RESULTS

The patient characteristics are shown in table 5.1. The age ranged from 20 to 58 years (mean ± standard deviation is 41.5 ± 9.9 yrs). No differences between men (n=32) and women (n=43) were found for any of the characteristics. The demographic features of this population did not differ from the reference population. Despite the normal level of employment in the patient

group (62.7% had work outside home), 13% and 25% of the patients were declared partially or completely incapacitated for work, in comparison with a total incapacity percentage of 9% within the reference population. This discrepancy is caused by the fact that 10 of the subjects who were declared partially or completely incapacitated for work were simultaneously involved in a pain occupation, and 2 were studying.

TABLE 5.1. Demographic patient characteristics

	HMSN patients (N=75)	
Mean age (mean ± sd)	41.5	(9.9)
Gender (N, %)		
male	32	42.7
female	43	57.3
Marital status (N, %)		
married/living together	50	66.7
living independently	20	26.6
living with parents	5	6.7
Higher education (>12 yrs) (N,%)	21	28.0
Current status of employment (N,%)		
work outside home	47	62.7
household	3	4.0
study/school	8	10.7

The mean values of the SIP-A, SIP-M and CIS-fatigue were significantly different for the patients compared to the healthy reference groups ($p < 0.05$). Patients experienced more ambulatory and mobility related disability and were less physically active, as measured by the actometer. The mean MRC scores of the lower extremity and the distal body-parts (both 3.3) showed a marked paresis and a high level of pain- discomfort (76%).

Twenty-one patients reported no ambulatory disabilities and 54 patients reported ambulatory disability scores ranging from 35 to 393 (table 5.2). The mean CIS fatigue score of the patients without ambulatory disability (28.5) indicated no severe fatigue. The mean actometer score of these patients (89.5) was comparable with the activity score of the healthy reference group (90.6).

The patient group which reported ambulatory disability was significantly older, had more mobility related disabilities, had less muscle strength, was less physically active, more fatigued and had a lower current perceived health state (VAS) compared to the group without ambulatory disability (table 5.2). No significant group differences were found for the self care, anxiety- depression, and pain- complaints items. A total of 71% of the patients without disability were involved in a paid occupation compared to 51% of the patients with ambulatory disability, which was not significantly different. The use of walking aids also differed: 24% of the patients without ambulatory disability used walking aids compared to 59% of the patients within the disability group.

TABLE 5.2. Outcome variables for the total patient sample (N=75) according to level of ambulatory disability

	Total (N=75)	**No ambulatory disability** (N=21)	**Ambulatory disability** (N=54)	**p-Value***
Age	41.5 (9.9)	36.5 (10.9)	44.6 (8.3)	0.001
Walking aids (%)	49	24	59	0.006
Employed (%)	62.7	71	51.9	ns
MRC Lower extremity (knee and ankle)	3.3 (1.2)	4.3 (1.0)	2.9 (1.1)	0.000
MRC Distal (ankle and hand)	3.3 (1.2)	4.2 (1.0)	2.9 (1.0)	0.000
SIP Mobility	22 (55) †	0 (0)	62.6 (8.5)	0.001
CIS Fatigue	35.0 (12.7)	28.6 (13.0)	37.5 (11.8)	0.006
Actometer	69.8 (22.4) †	89.5 (19.1)	62.1 (18.6)	0.000
Max walking duration ‡	41.3%	76%	29%	0.000
EuroQoL Self-care ‖	11%	0%	15%	ns
EuroQoL Pain- discomfort ‖	76%	62%	82%	ns
EuroQoL Anxiety- depression ‖	20%	19%	20%	ns
EuroQoL General Health status (VAS)	66.1 (19.7)	73.3 (18.0)	63.2 (19.9)	0.048

Data is presented as mean (± standard deviation), unless otherwise specified
* = Level of significance for group difference
† = Significantly different from reference group of healthy controls
‡ = Percentage of patients with an estimated maximum walking duration of > 1hr
‖ = Percentage of patients with a EuroQoL score of 2 or 3
ns = not significant, MRC= Medical Research Council, SIP= Sickness Impact Profile, CIS= Checklist Individual Strength, VAS=Visual Analogue Scale

By means of multiple linear regression analyses a total of 21.6% of the ambulatory disability in the patients with ambulatory disability was predicted. Of the variables that were entered (actometer score, CIS fatigue score, age, MRC distal, maximum walking duration), only the variables MRC distal and maximum walking duration had a significant contribution to the explained variance in ambulatory disability ($p=0.03$ and $p=0.005$, respectively). To verify the reported (dis)abilities (including estimated maximum walking duration) we assessed the actual level of physical activity by actometer. These variables showed a significant correlation of 0.452 ($p < 0.001$)).

Forty-nine percent of the total patient sample used walking aids (table 5.3). When analysing the mean scores, this group of patients was significantly older, had less muscle strength, was less physically active, more fatigued and reported more ambulatory and mobility related disabilities compared to the group of non-users. In contrast, no significant group differences were found for the participation and quality of life variables.

TABLE 5.3 Outcome variables for the total patient sample (N=75) according to the use of walking aids

	Total (N=75)	**No walking aids** (N=38)	**Walking aids** (N=37)	**p-Value***
Age	41.5 (9.9)	38.8 (10.3)	46.0 (7.8)	0.001
Employed (%)	62.7	63.2	62.2	ns
MRC Lower extremity (knee and ankle)	3.3 (1.2)	3.7 (1.2)	2.8 (1.1)	0.001
MRC Distal (ankle and hand)	3.3 (1.2)	3.7 (1.2)	2.8 (1.0)	0.001
SIP Ambulation	109 (101) †	72 (93)	147 (94)	0.001
SIP Mobility	22 (55) †	6 (31)	38 (68)	0.011
CIS Fatigue	35.0 (12.7)	31.3 (13.8)	38.8 (10.4)	0.009
Actometer	69.8 (22.4)†	75.8 (21.7)	63.6 (21.6)	0.018
Max walking duration ‡	41.3%	57.9%	24.3%	0.006
EuroQoL Self-care ‖	11%	5%	16%	ns
EuroQoL Pain- discomfort ‖	76%	68%	84%	ns
EuroQoL Anxiety- depression ‖	20%	18%	22%	ns
EuroQoL General Health status (VAS)	66.1 (19.7)	69.9 (20.7)	62.1 (18.4)	ns

Data is presented as mean (± standard deviation), unless otherwise specified
* = Level of significance for group difference
† = Significantly different from reference group of healthy controls
‡ = Percentage of patients with an estimated maximum walking duration of > 1hr
‖ = Percentage of patients with a EuroQoL score of 2 or 3
ns = not significant, MRC= Medical Research Council, SIP= Sickness Impact Profile, CIS= Checklist Individual Strength, VAS=Visual Analogue Scale

The relationship between ambulatory disability and the use of walking aids is further specified in table 5.4. In general, orthopedic shoes and canes were reported most often as a walking aid. The use of wheelchairs and walkers was limited and confined to the group of patients with ambulatory disability. For longer distances, 3 patients with ambulatory disability used an electrical wheelchair, 5 used a hand-rim propulsed wheelchair, and 2 used a walker.

TABLE 5.4. Specification of the use of walking aids

	Use of walking aids (N)		**Total**
	No	Yes	
No ambulatory disability *	16	5	21
Ambulatory disability	22	32	54
Total	38	37	75

	Ambulatory disability	
	No	Yes
Electrical wheelchair	0	3
Handrim propulsed wheelchair	0	5
Walker	1	2
Cane	1	12
Orthopaedic shoes	3	12
Total	5	32

N= number of patients, * Ambulatory disability is defined as SIP-A > 27.5

DISCUSSION

From this study we show that ambulatory and mobility related disabilities frequently occur within a large homogeneous population of HMSN I patients. Compared to healthy subjects, patients were more fatigued and experienced high levels of pain- discomfort. Actometer scores unequivocally showed that they were less physically active.
The patients with ambulatory disability had increased age, fatigue, degree of paresis, decreased physical activity, and a decreased general health status, compared to the patients without ambulatory disability. The patients who used walking aids were generally more severely affected compared to the patients without walking aids, according to their muscle strength, fatigue, physical activity and disability scores.
The use of walking aids in our patient sample (49%) was comparable with the percentage mentioned by Pfeiffer et al. (52%) (11). Although we found a higher use of walking aids in the group of patients who perceived ambulatory disability, the presence of perceived ambulatory disability did not distinguish walking aids users from non-users. Walking aids may have eliminated ambulatory problems in the group of users without perceived
ambulatory disability. However, 41% of the patients that perceived ambulatory disability did not use any form of walking aids, suggesting that the use of walking aids is currently not optimal. This could be explained, partly, by a lack of adequate prescription by practioners or by disacceptance and feelings of shame regarding the use walking aids within the patient group.
The patients' scores on perceived disability of both ambulation and mobility were significantly higher than the scores of the reference group of 90 healthy people. As for the perceived disabilities, our patient population reported more ambulatory than mobility related disabilities. Apparently, HMSN I patients mainly experience a deterioration of gait, whereas they are not so much limited in their ability to leave the house and join social activities. Probably, they are able to compensate adequately for their mobility problems, rather than for their walking problems.

The estimated walking duration was surprisingly consistent with the actometer score in our patient sample, as was shown by the correlation coefficient. It seems that HMSN I patients were able to judge their activities and capabilities rather well, which is in contrast with previous findings in other patient categories, such as survivors of cancer (24). Since HMSN is a genetic disorder, which progresses very slowly, it is suggested that these patients are able to adjust to their limitations very gradually, which enables them to make a rather accurate estimation about their current physical capabilities. The actometer score solely represents the physical activity of the lower extremity, so it is possible that the actometer score has slightly underestimated the physical activity of the patients who incidentally used a handrim propulsed wheelchair for longer distances (N=5).

The mean percentage of patients suffering from anxiety- depression, and the high level of pain-complaints (20% and 76%) were comparable to the percentages measured by Pfeiffer et al. (18% and 68%), and were not related to ambulatory disability or the use of walking aids (11). We also found a high level of fatigue, which is imaginable since HMSN patients have to compensate continuously in their postural control by extra muscular, visual and cognitive efforts. The mean

level of paid employment (63%) in our patient sample did not differ from the reference population and was not significantly related to the use of walking aids There was a trend, however, that patients without ambulatory disability were more often involved in a paid occupation compared to patients with significant ambulatory disability (71% vs 51%).

We found that the variables strength loss, physical activity and general health state differed between patients, based on the presence of ambulatory disability. However, we were not able to detect differences for the emotional aspects of quality of life, as shown by Teunissen et al. and Piccininni et al. in related patient groups suffering from an axonal polyneuropathy or hereditary neuromuscular disease in general (13,15). In the present study, the only measurement of emotional status was the item anxiety- depression of the EuroQoL. The mean score of our patient sample was low on this item, and there was small intersubject variability. The absence of substantial emotional suffering may explain the lack of significant differences between the patient groups.

Multiple regression analyses revealed the variables that were able to explain part of the reported ambulatory disability. Estimated maximum walking duration, which was also a self-reported measure, partly explained the level of perceived ambulatory disability. Apparently, patients were consistent in reporting their perceived (dis)abilities. The other variable that was able to explain part of the perceived ambulatory disability was the amount of strength loss on the distal body parts, as measured by the MRC. Future long-term follow-up research, with greater power, might shed more light on the main causes of ambulatory related disabilities. The high levels of pain-discomfort and fatigue need further scientific attention as well. Fatigue was recently investigated by Kalkman et al. in a study comparing patients with facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-I patients (25). They found that the perceived fatigue in HMSN-I patients was not clearly related to their functional impairments.

In conclusion, ambulatory disability frequently occurs, even in HMSN I patients who appear to walk relatively well. The presence of ambulatory disability is associated with increased age and fatigue, and decreased muscle strength, physical activity and perceived health state. Walking aids are generally administered to the more severely affected patients, however, the use of walking aids is not completely in accordance with the perceived disability. Thus, with respect to walking aids, counseling and prescription require specific care. In addition, physicians who attend to HMSN I patients should be observant to pain- discomfort and fatigue.

REFERENCES

1. Martini R, Berciano J, Van Broeckhoven C. 5th Workshop of the European CMT Consortium, 69th ENMC International Workshop: therapeutic approaches in CMT neuropathies and related disorders 23-25 April 1999, Soestduinen, The Netherlands. Neuromuscul Disord 2000; 10(1):69-74.
2. Gabreëls-Festen AA, Bolhuis PA, Hoogendijk JE, Valentijn LJ, Eshuis EJ, Gabreëls FJ. Charcot-Marie-Tooth disease type 1A: morphological phenotype of the 17p duplication versus PMP22 point mutations. Acta Neuropathol (Berl) 1995; 90(6): 645-649.
3. Krajewski KM, Lewis RA, Fuerst DR, et al. Neurological dysfunction and axonal degeneration in Charcot-Marie-Tooth disease type 1A. Brain 2000; 123.7: 1516-1527.
4. Garcia A, Combarros O, Calleja J, Berciano J. Charcot-Marie-Tooth disease type 1A with 17p duplication in infancy and early childhood: a longitudinal clinical and electrophysiologic study. Neurology 1998; 50(4): 1061-1067.
5. Berciano J, Garcia A, Combarros O. Initial semeiology in children with Charcot-Marie-Tooth disease 1A duplication. Muscle Nerve 2003; 27(1): 34-39.
6. Birouk N, Gouider R, Le Guern E, et al. Charcot-Marie-Tooth disease type 1A with 17p11.2 duplication. Clinical and electrophysiological phenotype study and factors influencing disease severity in 119 cases. Brain 1997; 120(5): 813-823.
7. Thomas PK, Marques W Jr, Davis MB, et al. The phenotypic manifestations of chromosome 17p11.2 duplication. Brain 1997; 120: 465-478.
8. Vinci P, Perelli SL. Footdrop, foot rotation, and plantarflexor failure in charcot-Marie-Tooth disease. Arch Phys Med Rehabil 2002; 83(4): 513-516.
9. Holmberg BH. Charcot-Marie-Tooth disease in northern Sweden: an epidemiological and clinical study. Acta Neurol Scand 1993; 87(5): 416-422.
10. Pfeiffer G, Wicklein EM, Ratusinski T, Schmitt L, Kunze K. Disability and quality of life in Charcot-Marie-Tooth disease type 1. J Neurol Neurosurg Psychiatry 2001; 70(4): 548-550.
11. MacMillan JC, Harper PS. The Charcot-Marie-Tooth syndrome: perceptions of disability and projected use of DNA diagnostic tests. Clin Genet 1992; 42(4): 161-163.
12. Teunissen LL, Eurelings M, Notermans NC, Hop JW, van Gijn J. Quality of life in patients with axonal polyneuropathy. J Neurol 2000; 247(3): 195-199.
13. Molenaar DSM, Vermuelen M, de Visser M, de Haan R. Impact of neurologic signs and symptoms on functional status in peripheral neuropathies. Neurology 1999; 52(1): 151-156.
14. Piccininni M, Falsini C, Pizzi A. Quality of life in hereditary neuromuscular diseases. Acta Neurol Scand. 2004; 109(2): 13-119.
15. Fowler WM, Abresch RT, Koch TR, Brewer ML, Bowden RK, Wanlass RL. Employment profiles in neuromuscular diseases. Am J Phys Med Rehabil 1997; 76(1): 26-37.
16. Medical Research Council. Aids to the examination of the peripheral nerve injuries. London: Her Majesty's Stationery Office, 1981:1.
17. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. The sickness impact profile; results of an evaluation study of the Dutch version. Ned Tijdschr Geneeskd 1990; 134(40): 1950-1954.
18. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19(8): 787-805.
19. van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49(5): 373-379.
20. Brooks R. EuroQol: the current state of play. Health Policy 1996; 37(1): 53-72.
21. de Boer AGEM, van Lanschot JJB, Stalmeier PFM, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004; 13: 311-320.

22. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
23. Vercoulen JH, Alberts M, Bleijenberg G. De checklist individual strength (CIS) [the checklist individual strength]. Gedragstherapie 1999; 32: 131-136.
24. Servaes P, Verhagen CA, Bleijenberg G. Relations between fatigue, neuropsychological functioning, and physical activity after treatment for breast carcinoma: daily self-report and objective behavior.Cancer 2002; 95(9): 2017-2026.
25. Kalkman JS, Schilling ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-I patients. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.

CHAPTER 6

Experienced and physiological fatigue in neuromuscular disorders

This chapter is submitted for publication as:
Schillings ML, Kalkman JS, Janssen HMHA, Bleijenberg G, van Engelen BGM, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders.

ABSTRACT

Objectives

Fatigue has been described as a typical symptom of various neurological diseases. It might be caused both by changes at the peripheral and at the central level. This study measured the level of experienced fatigue and physiological correlates of fatigue in three genetically defined neuromuscular disorders.

Methods

65 Facioscapulohumeral dystrophy (FSHD), 79 classical myotonic dystrophy (MD), 73 hereditary motor and sensory neuropathy type I (HMSN) patients and 24 age-matched healthy controls made a 2-min sustained maximal voluntary contraction of the biceps brachii muscle. Experienced fatigue at the current moment was assessed with the abbreviated fatigue questionnaire just before the physiological measurement. Peripheral fatigue was quantified by comparing the amplitudes of an initial and a final stimulated force response during rest. Muscle fibre conduction velocity was determined from a 5-channel surface EMG recording in order to show peripheral changes during the contraction. Central aspects of fatigue were measured using superimposed electrical endplate stimulation. Two weeks later, the Checklist Individual Strength subscale fatigue (CIS-fatigue) was used to determine the level of experienced fatigue of the past two weeks.

Results

Patients showed an increased level of experienced fatigue. Total physiological and peripheral fatigue were smaller in patients compared to controls, and central fatigue was normal. The most interesting result of this study was the presence of a large central activation failure (CAF) in all groups of neuromuscular patients; they showed CAF values of 36 - 41% already directly at the start of sustained contraction, whereas the control group showed only 12%. CAF slightly correlated with the level of experienced fatigue just before the test.

Conclusion

The cause of the large CAF in patients is unclear. Reduced concentration, motivation or effort can lead to lower central activation. In neuromuscular patients especially fear of physical activity or fear to damage the muscle or nerve tissue may contribute. Besides, also physiological feedback mechanisms or changes at the motocortical level may be a cause of reduced central activation.

INTRODUCTION

Fatigue is a typical symptom of various neurological diseases(9). It is present in more than 60% of patients with a neuromuscular disorder(21,32,41). In Parkinson's disease, more fatigue is associated with less physical activity, worse physical function, and lower functional capacity (17). In current literature, the term fatigue indicates both experienced fatigue and types of physiological fatigue.

Experienced fatigue has been defined as a difficulty in initiation of or sustaining voluntary activities (9). Krupp and Polina have described it to be an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion (27). The symptom is distinguished from weakness and does not necessarily correlate with signs of physiological fatigue (26,27).

Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force (15). It is divided into peripheral and central components, a division based on whether a loss of capacity to generate a maximum force originates in the muscle tissue or in the nervous system, respectively. During a sustained maximal voluntary contraction (MVC), healthy subjects develop both peripheral and central fatigue (23,46). The occurrence of central fatigue means that central activation worsens during the contraction. However, central activation is sub optimal already at the start of a sustained MVC (46).

Literature about physiological fatigability in neuromuscular patients is scarce. It is an interesting phenomenon, because the muscle itself - the motor of movement and force - is affected. McComas and co-workers have described that increased fatigability inevitably occurs in patients with muscle weakness, regardless whether the latter is due to a central or a peripheral neurological disorder (31). Not only (possibly indirect) peripheral changes, but also central changes could be responsible for this. Recently, alterations in the central nervous system have been described in neuromuscular disorders (10,11,14,28,36,40,53), but their influence on fatigue has not yet been studied.

The aim of the present study was to investigate both peripheral and central aspects of physiological fatigue during a sustained MVC in neuromuscular patients. We correlate these factors of physiological fatigue to the level of experienced fatigue just before the test. To get a broad overview of different types of neuromuscular disorders and to find possible disease specific mechanisms playing a role in the development of fatigue, we studied three genetically characterised neuromuscular disorders: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; hereditary motor and sensory neuropathy type Ia (HMSN), a neurogenic disorder; and myotonic dystrophy (MD), a multisystem disorder.

METHODS

Subjects

Age-matched groups of 65 FSHD-, 79 classical DM-, 73 HMSN-patients and 24 neurologically healthy controls participated in the study (Table 6.1). Patients registered in our hospital or at the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland, VSN) were

recruited. Only ambulant patients, age 18-60 years, able of passive abduction of the left shoulder to 90^0 were included.
Disease severity was determined with the Medical Research Council grading scale (MRC; 0 to 5) investigating the strength of the shoulder abductors, grip force, foot extensors and knee extensors. In order to characterise the patients, these eight values (both left and right) were averaged (Table 6.1). In order to verify the diagnoses, the patients' neurologists were contacted. In part of the patients, the diagnosis was genetically confirmed (Table 6.1).
The protocol was approved by the Committee on Research Involving Human Subjects Region Arnhem-Nijmegen. All subjects gave their written informed consent before participation.

TABLE 6.1 Details of subject groups

				Age			**Mean MRC**			**DNA**
	N total	men	women	mean	SD	range	mean	SD	range	confirmed
FSHD	65	58.5%	41.5%	43.1	10.3	22.5-60.9	3.6	0.8	1.9-5.0	83.1%
MD	79	55.7%	44.3%	41.0	9.8	22.5-56.6	3.7	0.8	2.0-5.0	62.0%
HMSN	73	41.1%	58.9%	42.4	9.8	20.0-58.0	3.7	0.9	1.5-5.0	45.2%
control	24	50.0%	50.0%	42.1	13.5	21.7-59.3	5.0	0.0	5.0-5.0	

Experienced fatigue
Just before the start of the physiological protocol, all patients and 16 controls filled out the 4-item abbreviated fatigue questionnaire (AFQ) (1) referring to the level of experienced fatigue at the current moment. Scores range from 4 to 28; higher scores indicate higher levels of fatigue. Fourteen days later, patients filled out the Checklist Individual Strength subscale fatigue (CIS-fatigue) evaluating the level of experienced fatigue during the past two weeks (43,55). Scores of this 8-item questionnaire range from 8 to 56. Values $\geq$ 35 indicate severe fatigue (49). Controls only answered the AFQ.

Physiological factors of fatigue
Experimental set-up
The experimental design has been used earlier in studies into peripheral and central aspects of fatigue in healthy subjects (46) and in patients with chronic fatigue syndrome (47). It is based on the twitch interpolation technique (35).
Subjects sat in a chair with their left arm fixed in a dynamometer in a horizontal position with the shoulder in abduction, the elbow in a right angle and the forearm supinated. Trunk and elbow were stabilised using common made pads. The force of elbow flexion was measured at the wrist. Force was sampled at a rate of 2 kHz and low-pass filtered (1 kHz). The maximal resolution of force measurement was 0.1 N bit (1).
Surface EMG (sEMG) was measured using a multi-electrode array of five gold-coated serrated electrodes (5) that were placed in line (electrode diameter 2 mm; inter electrode distance 3 mm) parallel to the fibre direction of the biceps brachii muscle, distal to the motor points. A reference electrode was placed at the elbow joint. Monopolar signals were amplified using a 64-channel amplifier system (MARK 6, Biosemi, Amsterdam, The Netherlands), band-pass filtered (3.2-800

Hz) and A/D-converted (16 bits with a resolution of 0.5 mV bit-1 at a rate of 4 kHz/channel). A custom-made time code generator synchronised force- and sEMG-data.
Using self-adhesive surface electrodes (Teca NCS2000 disposable surface electrode system) and a general-purpose electrical bio-stimulator (designed and manufactured by the local Department of Technical Engineering), electrical endplate stimulation was applied over the motor points of the medial and lateral head of the biceps brachii muscle (5). A stimulus event consisted of five times a 5-pulse 100-Hz train (duration 40ms). Pulse duration usually was 100μs. In 6 FSHD, 6 MD, 32 HMSN, and 1 control subject duration was set at 200 μs, because force responses to shorter stimulation were very low. The average of the five responses to these short trains is referred to as 'the force response' and is used for analysis. During voluntary contraction the inter-train interval was 300ms, during rest the inter-train interval was 1000ms. Pilot experiments had shown that these inter-train intervals were appropriate to avoid fusion of the single force responses.
Stimulus intensity was determined by increasing the current until the force did not rise anymore or until pain limited further increase. All SEs were given at this intensity level (FSHD: intensity mean 41.5, SD 10.5, range 20.0-72.9 mA; force mean 9.4, SD 4.6, range 1.9-18.4 N; MD: intensity mean 37.4, SD 11.0, range 19.9-88.4 mA; force mean 9.4, SD 5.0, range 1.4-25.9 N; HMSN: intensity mean 46.9, SD 9.7, range 26.0-65.7; force mean 7.2, SD 4.3, range 1.3-21.7 N; controls: intensity mean 44.0, SD 12.2, range 21.0-70.0; force mean 15.7, SD 6.5, range 8.2-31.3 N). The initial stimulus event was not preceded by a short voluntary contraction, because pilot experiments showed that potentiation did not occur with this type of stimulus event.

Protocol
The electrophysiological protocol has been described and visualised earlier (46,47). First, subjects made three short MVCs of the biceps brachii muscle with a 1-minute interval. After a 10-minute rest, an initial SE was applied while the subject's biceps brachii muscle was relaxed, resulting in the initial force response. Then, the subject performed a 2-minute sustained MVC of the biceps brachii muscle. SEs were given every 15s, leading to superimposed force responses. Verbal encouragement was given throughout and real-time visual feedback of the force was provided. Immediately after the sustained contraction, a final SE was applied while the muscle was relaxed, resulting in the final force response.

Force analysis
Voluntary force values are mean values over 2s of data just before stimulation, except for the value of MVC before the sustained contraction (MVCi), which is the true maximum. Values were obtained via Matlab6.5 (The Mathworks Inc., USA).
Physiological fatigue indicated the total amount of voluntary force lost during the sustained MVC: physiological fatigue = (1 - F120/F0) * 100%, in which F120 is the voluntary force at the end and F0 at the start of sustained MVC. A higher score indicates more fatigue.
Peripheral fatigue was determined by: peripheral fatigue = $(1 - F_s^e/F_s^b) * 100\%$, where F_s^b is the amplitude of the initial (before sustained MVC) and F_s^e the amplitude of the final (after sustained MVC) force response during rest. A higher score indicates a higher loss of force due to peripheral changes, and thus more peripheral fatigue.
Central activation failure (CAF) after *t* s of sustained MVC was calculated by:

$CAF^t = F_{sx}{}^t / (F_s{}^b - t/120 * (F_s{}^b - F_s{}^e)) * 100\%$, where $F_{sx}{}^t$ is the amplitude of the superimposed force response after *t* s from the start of sustained MVC. In calculating CAF^t, the influence of changing peripheral fatigue on the size of the superimposed force responses during MVC is taken into account, as described earlier(46). CAF was determined using Excel2000 (Microsoft Corporation®). A higher value of CAF indicates less central activation.
Central fatigue is defined as the change of CAF during the sustained MVC, thus:
central fatigue = CAF120 – CAF0. A higher score means that more fatigue occurs due to changes at the central level.

SEMG analysis
SEMG values used were calculated with Matlab6.5 (The Mathworks Inc., USA) from 2 s of data just before stimulation. As described in more detail before (46,47), muscle fibre conduction velocity (MFCV) was determined from four out of five electrodes. The upper limit of MFCV was set at 8 m s-1, based on physiological limits. MFCV is known to decrease with peripheral fatigue (35,56) and therefore used as a measure of peripheral fatigue during sustained MVC.

Statistical analysis
Differences between controls and the total group of patients were tested with an independent samples t-test. Possible differences between the three patient groups were analysed with one-way ANOVA (analysis of variance). The possible change of a variable during the sustained contraction was determined by linear regression. Slopes as well as the amount of peripheral fatigue were tested by one-sample t-tests.
In correlations in which MRC values were involved, Spearman's ρ was used. These were not calculated for healthy controls, because mean MRC is 5.0 in any control by definition. In other correlations, we used Pearson's coefficient (*r*). All statistical tests were performed with the Statistical Package for the Social Sciences (SPSS 12.0.1). Significance level was set at $p < 0.05$ (two-tailed). All values presented are means ± standard deviations.

RESULTS

Three subjects (2 HMSN and 1 DM) did not sustain the 2-minute MVC. Measurements of two FSHD subjects were stopped because the subjects fainted during detection of the motor points. Measurements of 1 FSHD and 1 DM patient failed because of technical problems. Of these seven subjects no force data was analysed. Electrical stimulation did not result in a sufficient force response in 4 FSHD, 6 DM and 17 HMSN patients. Although no stimulation data was available, other data of this group was used in further analyses.

Experienced fatigue
Answering the AFQ, patients reported a significantly higher level of current experienced fatigue than controls [Table 6.2, Fig. 6.1, AFQ: $t = 8.4$; $P < 0.001$]. There were no significant differences between the three patient groups. CIS-fatigue revealed high mean scores in patients for the level of experienced fatigue during the past two weeks [FSHD: 32.1 ± 11.7; DM: 34.1 ± 10.5; HMSN:

34.9 ± 12.9]. More than half of the patients showed CIS-fatigue ≥ 35, which is considered severely fatigued (49) [FSHD: 50.8%; DM: 53.2%; HMSN: 54.8%]. In all patient groups, AFQ values concerning the current fatigue level correlated significantly with the level of experienced fatigue during the past two weeks (CIS-fatigue) [FSHD: $r = 0.68$, $P < 0.001$; DM: $r = 0.53$, $P < 0.001$; HMSN: $r = 0.78$, $P < 0.001$].

TABLE 6.2. Force and fatigue values

	MVC, (N)	Experienced fatigue (AFQ)	Physiological fatigue (%)	Peripheral fatigue (%)	Central fatigue (%)	CAF_0 (%)
FSHD	133.5 ± 66.0	14.2 ± 5.7	29.3 ± 48.1	27.4 ± 24.0	4.5 ± 26.6	33.9 ± 23.7
MD	130.6 ± 64.9	16.1 ± 5.8	37.3 ± 33.4	29.5 ± 26.1	1.7 ± 26.6	41.4 ± 25.7
HMSN	148.3 ± 79.0	16.6 ± 6.3	36.3 ± 32.6	34.2 ± 24.8	15.1 ± 46.0	36.4 ± 23.4
control	209.8 ± 64.5	7.1 ± 3.7	54.3 ± 10.9	50.8 ± 13.7	3.9 ± 13.4	12.4 ± 10.7

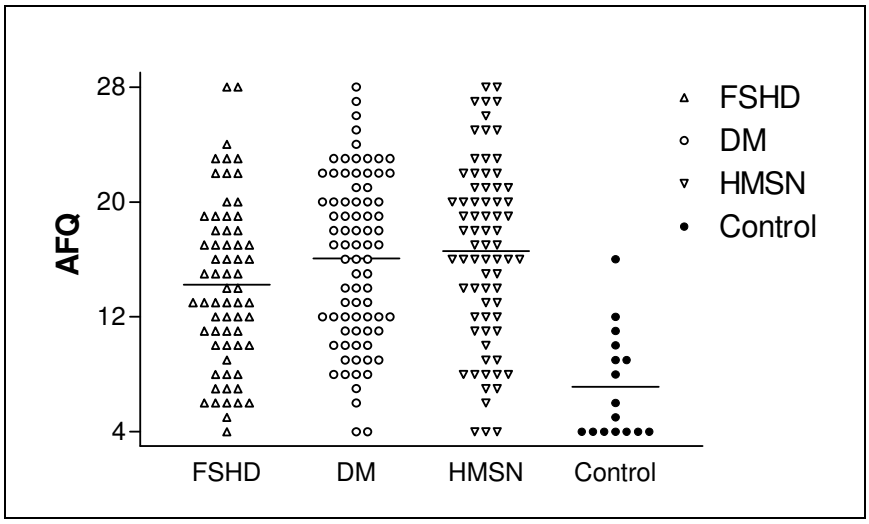

FIGURE 6.1. Level of experienced fatigue at the current moment measured with the AFQ just before the physiological protocol. Scores can range from 4 to 28. Higher scores indicate higher levels of experienced fatigue. Each symbol represents an individual subject. Horizontal lines show group averages. Patient groups clearly show higher mean values than the control group, although individual patients might have normal values.

Physiological fatigue

MVC of the biceps brachii muscle before sustained contraction (MVC_i) was significantly [$t = -4.8$; $P < 0.001$] lower in patients than in controls (Table 6.2). ANOVA showed no difference between the three patient groups. MVC at the start of sustained contraction (MVC_0) differed in the same way between the groups [$t = -5.9$; $P < 0.001$] (Fig. 6.2A). MVC_0 correlated negatively with AFQ scores in FSHD and HMSN [FSHD: $r = -0.29$, $P = 0.031$; HMSN: $r = -0.28$, $P = 0.024$].

In all groups, MVC declined significantly during the sustained contraction (FSHD: slope = -0.24 ± 0.39 %s-1, t = -4.7, P < 0.001; MD: slope = -0.27 ± 0.27 %s-1, t = -8.9, P < 0.001; HMSN: slope = -0.26 ± 0.23 %s-1, t = -8.9, P < 0.001; controls: slope = -0.44 ± 0.12 %s-1, t = -18.2, P < 0.001). This decline was slower in patients than in controls [t = 3.0; P = 0.003], but did not differ between the patient groups (Fig. 6.2A). Physiological fatigue, which is the size of the decline of voluntary force, was significantly larger in controls than in patients [t = -5.6; P < 0.001] and did not differ between the three patient groups. It correlated positively with mean MRC in all patient groups [FSHD: ϱ = 0.34, P = 0.010; MD: ϱ = 0.24, P = 0.035; HMSN: ϱ = 0.45, P < 0.001], and with AFQ in the HMSN group only [HMSN: r = -0.25, P = 0.043].

Peripheral fatigue

In all groups, the relative amplitude of the final force response - compared with the amplitude of the initial force response - showed that peripheral fatigue had occurred [FSHD: t = 8.7, P < 0.001; DM: t = 9.7, P < 0.001; HMSN: t = 10.3, P < 0.001, controls: t = 18.2, P < 0.001] (Table 6.2). Less peripheral fatigue occurred in patients than in controls [t = -6.2; P < 0.001], whereas the three patient groups did not differ.

The course of peripheral fatigue development during the sustained MVC, represented by MFCV values, is shown in Fig. 6.2B. All groups showed a negative slope not different between the groups (FSHD: slope = -0.013 ± 0.013 ms-2, t = -6.1, P < 0.001; MD: slope = -0.010 ± 0.008 ms-2, t = -9.7, P < 0.001; HMSN: slope = -0.011 ± 0.009 ms-2, t = -9.4, P < 0.001; controls: slope = -0.012 ± 0.008 ms-2, t = -7.1, P < 0.001). Peripheral fatigue correlated positively with mean MRC in FSHD [FSHD: ϱ = 0.27, P = 0.041]. It did not correlate with AFQ, neither in patients nor in controls.

Central activation failure and fatigue

At the start of the sustained MVC, patients showed higher CAF values than controls [t = 8.9; P < 0.001] (Fig. 6.2C, Fig. 3, Table 6.2). Values in the three patient groups were similar. CAF0 correlated negatively with mean MRC in FSHD and HMSN [FSHD: ϱ = -0.27, P = 0.038; HMSN: ϱ = -0.39, P = 0.004]. It correlated positively with AFQ in HMSN [r = 0.31, P = 0.022], but not in the other patient groups nor in the control group. Taking an average CAF of the first 30s MVC slightly reduced the variance of CAF values in controls, FSHD and MD. This CAF0-30 did correlate with AFQ scores in all three patient groups but not in controls, although P-values in FSHD were borderline [FSHD: r = 0.26, P = 0.051; MD: r = 0.27, P = 0.022; HMSN: r = 0.32, P = 0.019].

Only in the HMSN-group, the slope of CAF during the sustained contraction was significantly positive [slope = 0.10 ± 0.34 %s-1, t = 2.0, P = 0.046]. However, ANOVA did not show a difference between this slope and the slopes of the other patient groups. Slopes of patients and controls did not differ significantly. Central fatigue, measured as the difference of CAF120 and CAF0, was significantly positive in HMSN [t = 2.4, P = 0.019], and not in the other groups. Though, again ANOVA did not reveal a difference between the three patient groups and central fatigue was not different between patients and controls. In none of the groups central fatigue correlated with mean MRC or AFQ.

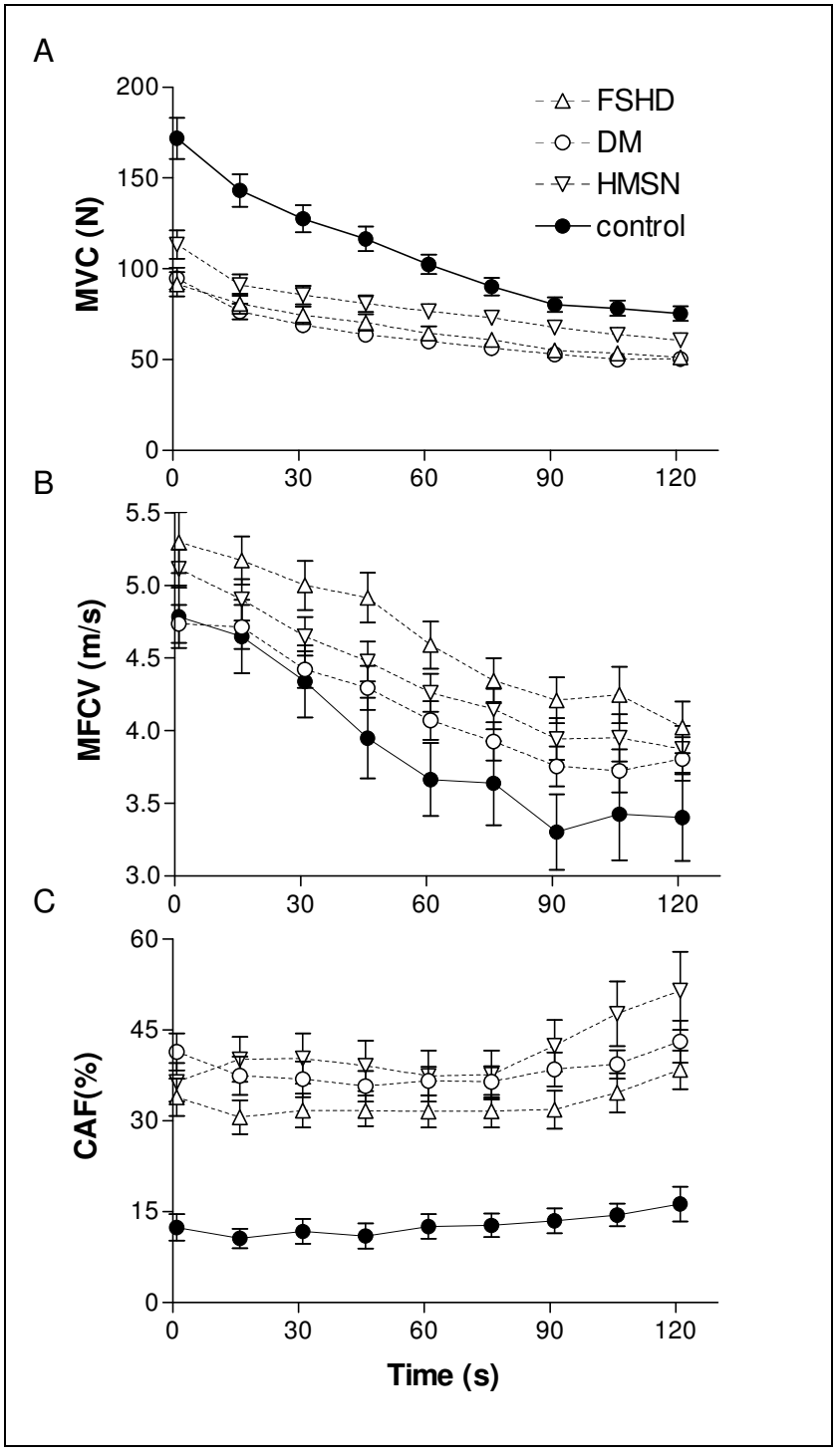

FIGURE 6.2. Voluntary force (A), muscle fibre conduction velocity (B) and central activation failure (C) during a 2-minute sustained MVC. At the start of the contraction, patients show lower voluntary force and higher central activation failure than controls. Voluntary force declines slower in patients than in controls.

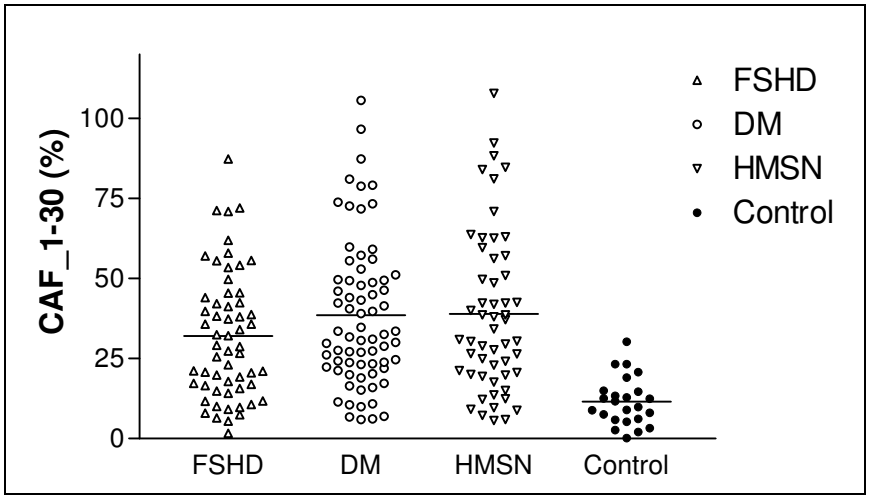

FIGURE 6.3. Central activation failure in FSHD-, DM-, and HMSN-patients, and healthy controls at the start of sustained MVC. Each symbol represents a mean CAF of the first 30 s MVC within one individual. Horizontal lines show group averages. Patient groups clearly show higher mean values than the control group, although individual patients might have normal values. Theoretically, CAF values lie between 0 and 100 %. In both DM and HMSN one artificially high value has been found, which must be ascribed to inaccuracy of the measurements.

DISCUSSION

This study shows that more than 50% of the neuromuscular patients has severe experienced fatigue. In a sustained MVC protocol, total physiological fatigue and peripheral fatigue are smaller in neuromuscular patients, but central fatigue is similar in patients and controls. Activation of the muscle by the central nervous system was shown to be less efficient in patients than in controls. The level of central activation failure correlated positively with the level of experienced fatigue. A remarkable similarity is present in all aspects of fatigue in the three groups of neuromuscular patients.

Experienced fatigue

Neuromuscular patients experience a high level of fatigue: patients' mean AFQ values were clearly higher than normal, both if compared to values measured in our control group and to reference values reported in literature (1). Correspondingly, CIS-fatigue scores of the neuromuscular patients were much higher than in the normal working population (4). The correlation between AFQ and CIS-fatigue showed that the level of experienced fatigue at the current moment parallels the level of long-term fatigue.

Peripheral fatigue

Smaller peripheral fatigability was present in patients compared to controls. This contrasts with the increased fatigability that was found during intermittent exercise in patients with amyotrophic lateral sclerosis (51), postpoliomyelitis syndrome (2,50) and multiple sclerosis (31,54). Schulte-Mattler and coworkers (48)described excessive peripheral fatigue during repetitive electrical

stimulation in mitochondrial encephalomyopathies and a hodgepodge of other neuromuscular disorders, among which FSHD, MD and a polyneuropathy. In contrast to our work, both the intermittent exercise tasks and the non-tetanic contractions after electrical stimulation avoid vascular occlusion.
In our protocol, blood flow will have been occluded less in the majority of patients than in the controls. This results from the lower intramuscular pressure, due to the smaller MVC in patients (56). The ongoing blood flow keeps the intracellular state in patients better than in controls. If our protocol had avoided vascular occlusion in both patients and controls, results on peripheral fatigability possibly would have been more in line with the literature.
Peripheral fatigue was not related to the current level of experienced fatigue.

Central activation failure and fatigue
Central fatigue was minimal in all groups. In contrast to our former studies (46,47), even healthy controls did show no central fatigue. This may have to do with the higher age of the newly studied group. How central fatigue relates to age, seems to be task-dependent and possibly also depends on the methodology used for CAF assessment (3). Our results do not show any relation between central and experienced fatigue, which is not surprising seen the very low central fatigue in all groups.
In contrast, CAF at the start of sustained MVC is enlarged in patients, and does relate to the level of experienced fatigue.
Of importance for the discrepancy between physiological fatigue measures and the level of experienced fatigue is the difference in concepts. Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force(15). In contrast, experienced fatigue has been characterised as a difficulty in initiation of or sustaining voluntary activities (9). It is a state not necessarily induced by exercise. CAF at the start of sustained contraction is neither influenced by exercise. This may explain why CAF correlates better to the level of experienced fatigue than the exercise-dependent physiological, peripheral and central fatigue.
As written above, CAF is higher in neuromuscular patients than in controls. This result seems to be in accordance with one of the findings of Di Lazzaro et al.(11).They showed an increased resting motor threshold in FSHD using transcranial magnetic stimulation (TMS), which might indicate lower resting membrane potentials of the cortical and/or spinal motoneurons (7). In contrast, Liepert and co-workers (28) did not observe a different motor threshold in a group of 10 myopathic patients, under whom 6 FSHD patients. TMS in MD patients neither showed a significant resting motor threshold alteration (40). Though, it demonstrated a prolongation of central motor conduction time in patients, which was related to motor threshold value (40).
Increased CAF also seems to contradict the lowered intracortical inhibition observed with TMS in FSHD and other myopathies (11,28). Enhanced excitability of α-motoneurons and increased amplitudes of motor-evoked potentials, described in myopathies by Liepert et al. (28), neither seem to be consistent with our results. However, the translation of results of isolated short-pulse TMS experiments into the behaviour of the brain in a more natural situation remains difficult. Apparently, although some systems possibly promote enhanced activation, in neuromuscular patients the output from the total chain of motor activation is reduced.

It is unclear which factors cause the reduced central activation in FSHD, MD and HMSN. In general, reduced concentration, motivation and effort increase CAFvalues (16,24,26,30). We tried to diminish the contribution of these factors by actively encouraging the subjects and by providing real-time visual feedback of the performance (52). Pain, described as a symptom of these neuromuscular disorders (6,8,42) or other feedback from muscles, joints and tendons may have reduced central activation (16, 18,44).

Although FSHD, MD and HMSN are most obviously characterized by muscle weakness, it cannot be excluded that other systems, including the (central) nervous system, are affected. In FSHD, the peripheral afferent sensory pathways (12), and in MD functioning of the sensory cortex have been shown to be altered (36). Functional changes at the motor cortical level have been described in several neuromuscular disorders (10.11.28,40). These may be a consequence of deconditioning or the relatively large demands on the affected neuromuscular system in daily life. It is well known that recruitment of motor units in neuromuscular disorders is abnormal. In myopathies more motor units are recruited already at low force levels; in neuropathies on the other hand, force is mainly regulated by control of firing rate (45). In both circumstances the activation pattern of the central nervous system may not be suited to counteract the peripheral problems, resulting in suboptimal drive.

The level of experienced fatigue and CAF are correlated, although explained variance is limited. This suggests that experienced fatigue influences CAF. Though, we cannot exclude the causality to be vice versa: CAF may (partly) control the experience of fatigue. In this light, it is interesting that patients with chronic fatigue syndrome, whose main complaint is the experience of severe fatigue, show enlarged CAF as well (26,47).

Finally, some pharmaceutical agents may influence CAF (22) by changing neuronal functioning. While about a third of our neuromuscular patients used any form of medication, we checked if this could explain the higher values of CAF in our group of patients. Sub group analyses, however, showed that CAF values of only medication-free patients were also increased.

Considering clinical practice, it is important to notice that MRC and MVC values can be strongly influenced by the amount of CAF. Reduced central activation further decreases the maximal voluntary force in neuromuscular patients who generally already have reduced muscle force because of changes in the muscle and/or nerve tissue. Therefore, these measures do not make an objective evaluation of neuromuscular functioning. Especially in weaker patients conclusions about muscle functioning should be drawn with great care, because CAF and mean MRC turned out to be negatively correlated in two of the three patient groups. How it influences the daily life of patients is unclear. Compared to controls, patients will more often need a higher percentage of MVC to perform daily tasks. However, a task, like the one we used, is uncommon in daily life. If central activation is also diminished during short contraction is formally unknown, but seems to be likely considering the large CAF at the start of sustained contraction. Resistance training has been suggested as a way to reduce CAF, but conclusive evidence has not yet been provided (reviewed by 62). However, results of Lindeman et al. (29) indeed strongly suggest a reduction of CAF during a training program in HMSN patients.

In conclusion, this paper shows that although neuromuscular patients experience considerably more fatigue than healthy controls, neither central nor peripheral fatigue is increased. Already at the start of sustained MVC, neuromuscular patients show diminished central activation, which is

correlated to the level of experienced fatigue. Right now, we can only speculate about the cause of this central activation failure. For clinical practice, it is important to bear the consequences in mind.

REFERENCES

1. Alberts M, Vercoulen JH, Bleijenberg G. Assessment of fatigue. The practical utility of the subjective feeling of fatigue in research and clinical practice. In: Vingerhoets A, editor. Assessment in behavioral medicine. Brunner Routledge; 2001. p. 301-27.
2. Allen GM, Gandevia SC, Neering IR, Hickie I, Jones R, Middleton J. Muscle performance, voluntary activation and perceived effort in normal subjects and patients with prior poliomyelitis. Brain 1994; 117 (Pt 4): 661-670.
3. Allman BL, Rice CL. Neuromuscular fatigue and aging: central and peripheral factors. Muscle Nerve 2002; 25: 785-796.
4. Beurskens AJ, Bultmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occup Environ Med 2000; 57: 353-357.
5. Blok JH, van Dijk JP, Drost G, Zwarts MJ, Stegeman DF. A high-density multichannel surface electromyography system for the characterization of single motor units. Rev Sci Instrum 2002; 73(4): 1887-1897.
6. Bushby KM, Pollitt C, Johnson MA, Rogers MT, Chinnery PF. Muscle pain as a prominent feature of facioscapulohumeral muscular dystrophy (FSHD): four illustrative case reports. Neuromuscul Disord 1998; 8: 574-579.
7. Caramia MD, Cicinelli P, Paradiso C, Mariorenzi R, Zarola F, Bernardi G *et al.* 'Excitability changes of muscular responses to magnetic brain stimulation in patients with central motor disorders. Electroencephalogr Clin Neurophysiol 1991; 81: 243-250.
8. Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtree LD, Beardsley RM *et al.* Neuropathic pain in Charcot-Marie-Tooth disease. Arch Phys Med Rehabil 1998; 79: 1560-1564.
9. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004; 363: 978-988.
10. D'Angelo MG, Bresolin N. Report of the 95th European Neuromuscular Centre (ENMC) sponsored international workshop cognitive impairment in neuromuscular disorders, Naarden, The Netherlands, 13-15 July 2001. Neuromuscul Disord 2003; 13: 72-79.
11. Di Lazzaro V, Oliviero A, Tonali PA, Felicetti L, De Marco MB, Saturno E *et al.* Changes in motor cortex excitability in facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2004; 14: 39-45.
12. Fierro B, Daniele O, Aloisio A, Buffa D, La Bua V, Oliveri M *et al.* Evoked potential study in facio-scapulo-humeral muscular dystrophy. Acta Neurol Scand 1997; 95: 346-350.
13. Fowler WM, Jr. Role of physical activity and exercise training in neuromuscular diseases. Am J Phys Med Rehabil 2002; 81: S187-S195.
14. Funakoshi M, Goto K, Arahata K. Epilepsy and mental retardation in a subset of early onset 4q35-facioscapulohumeral muscular dystrophy. Neurology 1998; 50: 1791-1794.
15. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001; 81: 1725-1789.
16. Gandevia SC, Allen GM, Butler JE, Taylor JL. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. J Physiol 1996; 490: 529-536.
17. Garber CE, Friedman JH. Effects of fatigue on physical activity and function in patients with Parkinson's disease. Neurology 2003; 60: 1119-1124.

18. Graven-Nielsen T, Lund H, Arendt-Nielsen L, Danneskiold-Samsoe B, Bliddal H. Inhibition of maximal voluntary contraction force by experimental muscle pain: a centrally mediated mechanism. Muscle Nerve 2002; 26: 708-712.
19. Herbert RD, Dean C, Gandevia SC. Effects of real and imagined training on voluntary muscle activation during maximal isometric contractions. Acta Physiol Scand 1998; 163: 361-368.
20. Iriarte J, de Castro P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. Eur J Neurol 1998; 5: 579-585.
21. Kalkman JS, van der Werf SP, van Engelen BGM *et al.* Fatigue complaints are equally characteristic for neuromuscular diseases as for multiple sclerosis. 2002. p. 779.
22. Kalmar JM, Cafarelli E. Effects of caffeine on neuromuscular function. J Appl Physiol 1999; 87: 801-808.
23. Kent-Braun JA. Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. Eur J Appl Physiol Occup Physiol 1999; 80: 57-63.
24. Kent-Braun JA, Le Blanc R. Quantitation of central activation failure during maximal voluntary contractions in humans. Muscle Nerve 1996; 19: 861-869.
25. Kent-Braun JA, Miller RG. Central fatigue during isometric exercise in amyotrophic lateral sclerosis. Muscle Nerve 2000; 23: 909-914.
26. Kent-Braun JA, Sharma KR, Weiner MW, Massie B, Miller RG. Central basis of muscle fatigue in chronic fatigue syndrome. Neurology 1993; 43: 125-131.
27. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 1996; 9: 456-460.
28. Liepert J, Schoser BG, Weiller C. Motor excitability in myopathy. Clin Neurophysiol 2004; 115: 85-89.
29. Lindeman E, Spaans F, Reulen J, Leffers P, Drukker J. Progressive resistance training in neuromuscular patients. Effects on force and surface EMG. J Electromyogr Kinesiol 1999; 9: 379-384.
30. Lloyd AR, Gandevia SC, Hales JP. Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome. Brain 1991; 114: 85-98.
31. McComas AJ, Miller RG, Gandevia SC. Fatigue brought on by malfunction of the central and peripheral nervous systems. Adv Exp Med Biol 1995; 384: 495-512.
32. Merkies IS, Schmitz PI, Samijn JP, van der Meche FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology 1999; 53: 1648-1654.
33. Merletti R, Knaflitz M, De Luca CJ. Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions. J Appl Physiol 1990; 69: 1810-1820.
34. Merton P. Voluntary strength and fatigue. J Physiol 1954; 123: 553-564.
35. Miller TA, Allen GM, Gandevia SC. Muscle force, perceived effort, and voluntary activation of the elbow flexors assessed with sensitive twitch interpolation in fibromyalgia. J Rheumatol 1996; 23: 1621-1627.
36. Mochizuki H, Hanajima R, Kowa H, Motoyoshi Y, Ashida H, Kamakura K *et al.* Somatosensory evoked potential recovery in myotonic dystrophy. Clin Neurophysiol 2001; 112: 793-799.
37. Newham DJ, Davies JM, Mayston MJ. Voluntary force generation and activation in the knee muscles of stroke patients with mild spastic hemiparesis. J Physiol 1995; 483.P: 128P.
38. Norregaard J, Bulow PM, Danneskiold-Samsoe B. Muscle strength, voluntary activation, twitch properties, and endurance in patients with fibromyalgia. J Neurol Neurosurg Psychiatry 1994; 57: 1106-1111.
39. Norregaard J, Bulow PM, Vestergaard-Poulsen P, Thomsen C, Danneskiold-Samoe B. Muscle strength, voluntary activation and cross-sectional muscle area in patients with fibromyalgia. Br J Rheumatol 1995; 34: 925-931.

40. Oliveri M, Brighina F, La Bua V, Aloisio A, Buffa D, Fierro B. Magnetic stimulation study in patients with myotonic dystrophy. Electroencephalogr Clin Neurophysiol 1997; 105: 297-301.
41. Paul RH, Cohen RA, Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenia gravis. Muscle Nerve 2000; 23: 1402-1406.
42. Phillips MF, Mathieu J. Physical disability in myotonic dystrophy. In: Harper PS, van Engelen BGM, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. New York: Oxford University Press; 2004. p. 68-82.
43. Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL *et al.* Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-847.
44. Rutherford OM, Jones DA, Newham DJ. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. J Neurol Neurosurg Psychiatry 1986; 49: 1288-1291.
45. Sanders DB, Stalberg EV, Nandedkar SD. Analysis of the electromyographic interference pattern. J Clin Neurophysiol 1996; 13: 385-400.
46. Schillings ML, Hoefsloot W, Stegeman DF, Zwarts MJ. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. Eur J Appl Physiol 2003; 90: 562-568.
47. Schillings ML, Kalkman JS, van der Werf SP, van Engelen BGM, Bleijenberg G, Zwarts MJ. Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. Clin Neurophysiol 2004; 115: 2518-2524.
48. Schulte-Mattler WJ, Muller T, Deschauer M, Gellerich FN, Iaizzo PA, Zierz S. Increased metabolic muscle fatigue is caused by some but not all mitochondrial mutations. Arch Neurol 2003; 60: 50-58.
49. Servaes P, van der WS, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. Support Care Cancer 2001; 9: 11-17.
50. Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Excessive muscular fatigue in the postpoliomyelitis syndrome. Neurology 1994; 44: 642-646.
51. Sharma KR, Kent-Braun JA, Majumdar S, Huang Y, Mynhier M, Weiner MW *et al.* Physiology of fatigue in amyotrophic lateral sclerosis. Neurology 1995; 45: 733-740.
52. Shield A, Zhou S. Assessing voluntary muscle activation with the twitch interpolation technique. Sports Med 2004; 34: 253-267.
53. Sigford BJ, Lanham RA, Jr. Cognitive, psychosocial, and educational issues in neuromuscular disease. Phys Med Rehabil Clin N Am 1998; 9: 249-270.
54. van der Werf SP, Jongen PJ, Nijeholt GJ, Barkhof F, Hommes OR, Bleijenberg G. Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities and neurological disability. J Neurol Sci 1998; 160: 164-170.
55. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
56. Zwarts MJ, Arendt-Nielsen L. The influence of force and circulation on average muscle fibre conduction velocity during local muscle fatigue. Eur J Appl Physiol Occup Physiol 1988; 58: 278-283.

CHAPTER 7

Determinants of experienced and physiological fatigue in patients with Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I

This chapter is submitted for publication as:
Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Determinants of experienced fatigue and physiological fatigue in patients with Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I.

ABSTRACT

Objectives

Fatigue is a common symptom in neuromuscular disorders. Little is known about different types of fatigue among patients with various neuromuscular disorders. Therefore, various determinants of experienced fatigue and physiological fatigue were assessed in three relatively common types of neuromuscular disorders

Methods

217 patients (65 Facioscapulohumeral Dystrophy, 79 adult-onset Myotonic Dystrophy, and 73 Hereditary Motor and Sensory Neuropathy type I patients) were studied. Experienced fatigue severity was assessed with the Checklist Individual Strength (CIS-fatigue). Physiological fatigue was measured during a 2-minute sustained maximal voluntary contraction of the biceps brachii muscle using the twitch interpolation technique to assess peripheral fatigue and central activation failure (CAF). A multidimensional assessment method was used including self-report questionnaires, a daily Self Observation List, physical activity (actometer), and neuro-psychological tasks. Muscle strength was determined with the Medical Research Council (MRC) scale.

Results

Experienced fatigue was significantly related to CAF, but not to peripheral fatigue. Regression analyses indicated that in FSHD psychological distress and sleep disturbances, in MD sleep disturbances, and in HMSN sleep disturbances and concentration problems significantly contributed to experienced fatigue. In FSHD pain contributed significantly to CAF. In FSHD and HMSN functional impairments in daily life contributed significantly to peripheral fatigue, in MD sleep disturbances and pain.

Conclusion

Fatigue in neuromuscular disorders is a complex concept with involvement of dimensions. Even between the various neuromuscular diseases studied, different variables contributed to its presence.

INTRODUCTION

Fatigue has been described with various definitions and descriptions that range from tiredness, sleepiness, and weakness to exhaustion(1). In current literature, the term fatigue refers both to experienced fatigue and to physiological fatigue.

Experienced fatigue has been defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion. It is not the same as muscle weakness or muscle fatigability (1). This type of fatigue is a common symptom of various neurological disorders and is most studied in multiple sclerosis, Parkinson's disease, and after a stroke[2-6]. Experienced fatigue is present in more than 60% of patients with various neuromuscular disorders and was associated with higher levels of functional impairments in daily life (7-11).

Our research group has developed a multidimensional assessment method to measure experienced fatigue in several chronic disorders (12-15). This multidimensional assessment method identifies various dimensions relevant for fatigue: functional impairment in daily life, physical activities, psychological distress, sleep disturbances, concentration problems, social functioning/social support, self-efficacy, and causal attributions. In chronic disorders like neuromuscular disorders also pain and muscle strength are assessed.

Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force and is divided into peripheral and central components (16). This division is based on whether a loss of capacity to generate a maximum force is found to originate in the muscle tissue or in the nervous system, respectively. During a sustained maximal voluntary contraction, healthy subjects develop both peripheral and central fatigue (17,18). The occurrence of central fatigue means that central activation worsens during the contraction. In healthy subjects central activation is sub optimal already at the start of a sustained maximal voluntary contraction (17).

Literature about the relation between experienced fatigue and physiological fatigue is lacking. Especially in neuromuscular disorders fatigue may be caused by peripheral and/or central dysfunction. Although there is an increasing knowledge of the physiology of peripheral and central fatigue, most studies are conducted in healthy controls. In this study we investigated besides experienced fatigue the relation between experienced fatigue, and physiological fatigue in neuromuscular patients. Physiological fatigue was divided in central activation failure (CAF) and peripheral fatigue.

In this study the contribution of the dimensions of experienced fatigue and disease severity was assessed in three homogeneous populations of patients with three relatively common, genetically well-defined neuromuscular disorders, namely: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; adult-onset myotonic dystrophy (MD), a multisystem disorder; and hereditary motor and sensory neuropathy type I (HMSN), a neurogenic disorder. To get an overview of different types of fatigue, we studied the determinants of experienced fatigue and of physiological fatigue.

As far as we know these different types of fatigue have never been studied simultaneously in neuromuscular disorders.

The first aim of the present study was to investigate the strength of the relationship between experienced fatigue, CAF and peripheral fatigue. The second aim was to examine the

determinants of the different types of fatigue (experienced fatigue, CAF, and peripheral fatigue) in the various neuromuscular disorders.

METHODS

Patients

Adult patients with a definite diagnosis of a neuromuscular disorder who could be classified into one of the following diagnostic categories were asked to participate: (1) facioscapulohumeral muscular dystrophy (FSHD), (2) adult-onset myotonic dystrophy (MD) or (3) hereditary motor and sensory neuropathy type I (HMSN-I). They were recruited from the outpatient clinic of the Neuromuscular Centre, based at the Institute of Neurology of the Radboud University Nijmegen Medical Centre and from the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland, VSN).

In total, 900 patients were informed by a letter and received a booklet with questionnaires at home. From the 647 adult patients (72%) who returned the questionnaires, 49 patients were excluded. In all, 598 patients fitted the diagnostic inclusion criteria and completed the questionnaires (66%). This group consisted of 139 patients with FSHD, 322 with MD, and 137 with HMSN-I.

For this study only ambulatory patients with age between 18-60 years were included. For the physiological measurement it was necessary that patients were able of passive abduction of the left shoulder to 90^0. From the 527 patients that were eligible 331 patients were willing to participate in this research project, but ultimately from 217 patients (65 FSHD, 79 MD and 73 HMSN patients) complete data could be collected. Patients dropped out for several reasons: large travel distance, inability to take a day off or personal reasons. The patients who refused to take part in the study did not differ from the participating subjects with regard to age, gender, marital status, level of education, and employment status and level of experienced fatigue in each neuromuscular disorder. Written informed consent was obtained from all participating patients. The regional ethics committee approved the study.

Procedure

The patients who agreed to take part in the study were invited to the Radboud University Nijmegen Medical Centre for the assessments. On the first day the physiological measurement was carried out. At home, they started with the daily Self Observation List (SOL) during a period of 12 days. Severity of experienced fatigue was reported four times a day in this list. Furthermore, quality of sleep, level of activity, hours of household activities and hours of work outside the house were reported once a day. During this period the patients were wearing an actometer. After this 12-day period, patients filled out several computerised questionnaires.

Physiological fatigue (CAF and peripheral fatigue)

Physiological measurements were used to determine peripheral fatigue and central activation failure (CAF). The experimental design was used earlier in studies into peripheral and central

aspects of fatigue in healthy subjects (18) and in patients with chronic fatigue syndrome (19). It was based on the twitch interpolation technique(16-20).
In short, subjects made a 2-minute sustained maximal voluntary contraction of the biceps brachii muscle. Electrical stimulation was applied before, just after and every 15 seconds during MVC. Each stimulus event consisted of 5 times a 5-pulse 100 Hz stimulustrain applied to the motor points. The average force response was used in analysis.
The difference in force response during rest before and after sustained MVC is used as a measure for peripheral fatigue. Superimposed force responses during MVC indicated the level of central activation failure. Namely, if voluntary muscle activation is optimal, electrical stimulation will not induce a force increase. If, however, a failure of voluntary central drive is present, electrical stimulation will lead to a superimposed force response.

Experienced fatigue
The Checklist Individual Strength (CIS) is a 20-item questionnaire and measures the following four aspects of fatigue during the previous two 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 high level of experienced fatigue, a high level of concentration problems, low motivation and low levels of activity (13,21). A CIS-fatigue score equal or higher 35 was used to identify severe fatigue (22). In addition, fatigue was measured with the Daily Observed Fatigue (DOF) score of the Self Observation List (SOL). Severity of fatigue was reported four times a day on a 5-point scale (0-4). Total scores range from 0 to 16.

Functional Impairment
The Sickness Impact Profile (SIP) was used to assess functional disability in the following 12 areas: sleep/rest, emotional behaviour, body care and movement home management, mobility, social interactions, ambulation, alertness behaviour, communication, work limitations, recreation and pastimes and eating (23,24). Higher score indicate a higher level of functional disability. In addition, daily worked hours (outside the home and household activities) were registered in the SOL.

Physical activity
The level of physical activity was assessed using an actometer (Actilog V3.0), a device worn by the patients around the ankle for 12 consecutive days (25). The actometer measures the number of accelerations over a 5-minute period. A general physical activity score is calculated by averaging the number of accelerations over the 12-day period (25). During this period of 12 days the patients filled out daily Self Observation List (SOL). Physical activity was registered once a day in the SOL. In addition, the subscales mobility and ambulation of the SIP were used.

Psychological distress
Psychological distress was measured with the Beck Depression Inventory for primary care (BDI-pc), and the Symptom Checklist-90 (SCL-90). The BDI-pc instead of the complete BDI, was used in order to prevent an overlap between physical aspects of fatigue with the somatic

symptoms of depression (26,27). This shortened version of the BDI has 7 items and is including cognitive and affective symptoms. A score of 4 or more is indicative of clinical depression. The SCL-90 indicates psychological distress for anxiety, agoraphobia, depression, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity, hostility and sleep disturbances (28). Higher SCL-subscale scores indicate more distress.

Sleep disturbances

Sleep disturbances were measured with the sleep/rest scale of the SIP and the sleep subscale of the SCL-90. Finally, quality of sleep (general quality of sleep, difficulties falling asleep, restless sleep, non restorative sleep, and early awakening) was registered daily in the SOL.

Concentration problems

Experienced concentration problems were measured with the concentration subscale of the CIS and the alertness behaviour subscale of the SIP. Neuropsychological performance was measured with the Complex Reaction Time Task (CRT) and the Symbol Digit subtest of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) (29,30). The CRT measures the speed of information processing and is comprised of three succeeding tasks, each providing a reaction time (RT) and movement time (MT). RT reflects speed of information processing and MT reflects motor speed. The Symbol Digit subtest (SDT) of the WAIS assesses the ability to concentrate. This test consists of pairing numbers with nonsense symbols as quickly as possible. The higher the score on this test, the better a person is able to concentrate.

Social functioning and social support

Social functioning was measured with the social interaction subscale of the SIP. Social support was measured by the van Sonderen Social Support Inventory (SSL) (31). The SSL was divided into the SSL-I (amount of social support), the SSL-D (discrepancies between amount of social support and desired amount of social support), and the SSL-N (amount of negative interactions). Total scores of SSL-I and SSL-D range from 34-136, total score of SSL-N from 7-28.

Self-efficacy

Self-efficacy, a sense of control over fatigue symptoms, was measured with the Self-efficacy Scale. The SES consisted of seven questions that measured sense of control with respect to fatigue (32). The total score ranges from 7 to 28, a higher score reflecting more sense of control.

Causal attribution

Causal Attribution with regard to fatigue complaints was measured with the Causal Attribution List (CAL). This questionnaire consisted of 4 items divided over two subscales; psychological related attributions and neuromuscular disorder related attributions. For each item, patients were asked to indicate their opinion regarding the cause of their fatigue complaints on a 4-point scale, a higher score indicating stronger causal attributions (32).

Muscle strength
Muscle strength was determined using the Medical Research Council (MRC) grading scale (MRC; 0 to 5) investigating the strength of the shoulder abductors, grip force, foot extensors and knee extensors (33). In order to characterise the patients, these eight values (both left and right) were averaged.

Pain
Pain intensity was assessed by a 0 – 100 rating Visual Analogue Scale (VAS) of average pain intensity on current moment, where 0 = no pain and 100 = pain as bad as could be. In addition, pain was measured with the daily-observed pain score of the SOL. Severity of pain was reported four times a day on a 5-point scale (0-4). Total scores range from 0 to 16.

Statistics
Data analysis was performed using SPSS (version 12.0). Descriptive statistics were used for description of the sample. T-tests, chi-square, analyses of variance (ANOVA) with correction according to Bonferroni multiple-comparison test and general linear model (GLM)-general factorial were performed to test differences between groups. P values < 0.05 were regarded as statistically significant. Correlations were calculated with the Spearman coefficient (r) correlation. In order to examine the contribution of the various dimensions of fatigue to the dimension of fatigue severity, linear regression analyses (enter-method) were performed. Regression analyses have been performed to examine the contribution of CAF and peripheral fatigue to experienced fatigue severity. Furthermore, regression analyses have been performed to examine the contribution of the dimensions and pain and disease severity to experienced fatigue severity. Two analyses were performed, one with the CIS-fatigue severity score as the dependent variable, and the other using the DOF score as the dependent variable. Independent variables were those questionnaires or subscales within the various dimensions that correlated strongest and significant with the dependent variable.
Finally, regression analyses have been performed to examine the contribution of the dimensions to physiological fatigue. Two analyses were carried out, one with the CAF score as the dependent variable, and the other using the peripheral fatigue score as the dependent variable.

RESULTS

The patient sample consisted of 65 FSHD patients, 79 MD patients, and 73 HMSN patients. Neuromuscular diagnoses of the patients were verified according to established criteria [34]. Demographic characteristics of the groups are summarized in Table 7.1. No significant differences were found in age, gender, marital status and level of education between the three groups.

TABLE 7.1. Demographic characteristics of the three neuromuscular patient groups

	FSHD n=65 mean (sd)	**MD** n=79 mean (sd)	**HMSN-I** n=73 mean (sd)
Mean age	43.1 (10.3)	41 (9.9)	42.4 (9.8)
Age range	22-60	22-56	20-58
Gender (male/female)	59% / 41%	56% / 44%	41% / 59%
Marital status			
married/living together	52 (80%)	53 (67%)	49 (68%)
divorced	3 (5%)	4 (5%)	4 (5%)
widowed	2 (3%)	---	4 (5%)
living independent	6 (9%)	13 (17%)	11 (15%)
living with parents	2 (3%)	9 (11%)	5 (7%)
Higher education (>= 12 years)	18 (28%)	17 (21%)	20 (27%)

Relation between experienced fatigue and physiological fatigue (CAF and peripheral fatigue)

In all patients (n=217) regression analyses showed that with the CIS-fatigue as dependent variable the CAF contributed significantly (beta=0.129, p=0.005), but peripheral fatigue did not contribute significantly (beta=0.075, p=0.396) to the experienced fatigue severity. In total, 4% of the experienced fatigue severity was predicted. In the analysis with the daily-observed fatigue (DOF) as dependent variable, the CAF contributed also significantly to the experienced fatigue (beta=0.314, p=0.000) and peripheral fatigue did not (beta= -0,032, p=0.711). In total, 10% of the DOF was predicted. No differences in physiological fatigue were found between severely fatigued and non-severely fatigued patients (Table 7.2).

Differences and similarities between the three neuromuscular disorders

The three groups were comparable concerning their functional limitations, psychological distress, and muscle force. However, MD patients reported more communication problems and more limitations in sleep and rest, while HMSN patients reported more sleep problems. The HMSN patients had significant higher levels of physical activity (mean actometer) than the two other groups. The MD patients reported more discrepancies between the amount of social support and desired amount social support (SSL-D) than the two other groups. Further, the MD patients reported significantly lower sense of control of fatigue symptoms (self-efficacy) and reported significantly less pain than FSHD and HMSN patients.

Determinants of experienced fatigue

Being severely experienced fatigued was associated with more problems in all dimensions (Table 7.2). The less fatigued FSHD, MD and HMSN patients had comparable scores, while the fatigued MD patients reported more limitations in sleep and rest, and reported more problems with communication. In the MD group, there were no differences in activity level between the experienced fatigued and non-experienced fatigued patients.

TABLE 7.2. Comparisons between severely experienced fatigued and non-severely experienced fatigued patients between the three neuromuscular disorders in physiological fatigue, dimensions of experienced fatigue, and disease severity.

	FSHD Severely fatigued N=33 mean (sd)	**FSHD** Non-severely fatigued N=32 mean (sd)	**MD** Severely fatigued N=42 mean (sd)	**MD** Non-severely fatigued N=37 mean (sd)	**HMSN** Severely fatigued N=40 mean (sd)	**HMSN-I** Non-severely fatigued N=33 mean (sd)	Sign. testing
I. Physiological fatigue							
CAF	33.2 (20.5)	30.9 (19.3)	43.6 (23.6)	33.4 (21.2)	41.3 (26.8)	36.4 (23.1)	
Peripheral fatigue	25.3 (22.1)	29.6 (25.9)	28.2 (25.5)	32.1 (26.5)	35.8 (24.9)	35.3 (23.2)	
II. Dimensions:							
1) Functional impairment in daily life							
SIP-household management	106.6 (96.1)	85.4 (93.7)	145.7 (100.1)	81.6 (71.1)	116.2 (106.4)	85.8 (94.6)	2
SIP-work problems	109.2 (130.8)	67.1 (130.2)	116.8 (122.0)	100.9 (142.1)	101.2 (137.7)	66.4 (116.5)	
SIP-recreation and pastime	76.6 (65.0)	38.3 (52.1)	100.8 (79.6)	49.2 (56.9)	86.1 (67.5)	21.3 (34.6)	2
SIP-body care and movement	160.8 (177.3)	81.3 (124.8)	221.5 (229.9)	135.9 (182.1)	210.9 (167.0)	120.2 (117.2)	2
SIP-communication	47.8 (66.8)	17.7 (40.3)	127.7 (124.7)	68.1 (93.5)	38.5 (38.5)	40.9 (63.1)	1, 2
SIP-eating	8.7 (24.9)	0	9.1 (24.5)	2.6 (11.2)	1.9 (8.2)	2.4 (9.6)	2
Daily worked hours (SOL)	2.3 (2.2)	3.7 (2.6)	3.1 (2.2)	2.1 (2.2)	2.2 (2.2)	2.9 (3.0)	3
Daily houshold hours (SOL)	2.0 (1.4)	1.5 (1.3)	1.3 (1.1)	1.8 (1.4)	1.7 (1.6)	1.9 (1.4)	
2) Physical activities							
SIP-mobility	32.3 (66.0)	26.0 (55.6)	41.9 (74.2)	34.2 (75.6)	23.6 (58.5)	18.4 (50.1)	
SIP-ambulation	139.7 (100.0)	92.8 (112.4)	133.9 (119.1)	93.3 (101.9)	124.9 (97.7)	81.3 (97.2)	2
Mean actometer	52.6 (15.2)	61.5 (21.6)	56.9 (24.6)	61.6 (20.7)	64.8 (18.9)	77.2 (24.5)	1,2
Daily activity score (SOL)	5.3 (1.5)	6.0 (1.9)	4.8 (1.6)	4.9 (1.8)	5.6 (1.8)	6.3 (2.3)	1,2
3) Psychological distress							
BDI-PC	1.6 (2.4)	0.5 (0.7)	1.4 (1.6)	0.8 (1.3)	1.9 (3.1)	0.5 (0.9)	2
SCL-anxiety	13.6 (5.8)	10.9 (1.3)	12.0 (2.5)	12.0 (5.0)	14.8 (6.7)	12.0 (2.1)	2
SCL-agoraphobia	9.1 (4.5)	7.5 (1.2)	7.6 (1.3)	7.7 (1.6)	8.2 (3.0)	7.6 (1.3)	
SCL-depression	24.6 (10.9)	18.1 (2.3)	23.4 (5.3)	19.6 (4.6)	25.9 (11.8)	19.8 (5.0)	2
SCL-somatisation	22.0 (7.4)	16.0 (3.7)	20.2 (5.3)	17.5 (4.5)	23.4 (6.2)	16.8 (3.8)	2
SCL-obsess.-comp. behaviour	15.6 (7.9)	11.4 (2.6)	16.2 (4.7)	13.3 (4.3)	16.0 (5.7)	11.3 (2.0)	2
SCL-interpersonal sensitivity	25.6 (11.1)	21.0 (4.4)	24.8 (6.2)	23.8 (7.4)	26.4 (9.9)	22.5 (6.5)	2
SCL-hostility	7.5 (2.5)	6.5 (1.1)	7.0 (1.5)	6.8 (1.7)	7.5 (2.6)	6.8 (1.2)	2
SIP-emotional behaviour	50.1 (80.4)	10.4 (29.8)	19.8 (35.9)	14.1 (39.5)	51.3 (52.8)	15.8 (36.1)	2
CIS-motivation	12.4 (5.3)	8.8 (3.8)	15.9 (5.7)	12.0 (5.0)	12.4 (5.5)	8.7 (3.6)	1,2

Main effects: 1=group membership is significant, 2= fatigued vs. non-fatigued is significant. Interaction effect: 3= group x fatigue interaction effect is significant.

[1)] for FSHD n= 52, MD n=68, and HMSN n=60 (these questionnaires have not been filled out by those patients who reported that they never experience fatigue)

TABLE 7.2. Comparisons between severely experienced fatigued and non-severely experienced fatigued patients between the three neuromuscular disorders in physiological fatigue, dimensions of experienced fatigue, and disease severity.

	FSHD Severely fatigued N=33 mean (sd)	**FSHD** Non-severely fatigued N=32 mean (sd)	**MD** Severely fatigued N=42 mean (sd)	**MD** Non-severely fatigued N=37 mean (sd)	**HMSN** Severely fatigued N=40 mean (sd)	**HMSN-I** Non-severely fatigued N=33 mean (sd)	Sign. testing
4) Sleep disturbances							
SIP-sleep/rest	51.3 (56.0)	31.1 (38.2)	94.1 (74.2)	44.1 (39.1)	77.2 (59.2)	30.2 (45.0)	1,2
SCL-sleep	4.6 (2.4)	4.2 (1.8)	4.2 (1.6)	3.8 (1.6)	6.0 (2.7)	4.4 (1.6)	1
% daily general quality of sleep	67.4 (26.2)	76.6 (24.7)	69.4 (23.9)	82.0 (21.2)	55.2 (24.8)	75.8 (26.0)	1,2
% daily restless sleep	21.7 (21.3)	13.8 (20.6)	18.5 (17.0)	9.1 (13.1)	33.1 (22.0)	21.0 (20.5)	1,2
% daily early awakening	11.1 (17.1)	12.8 (22.1)	7.3 (12.9)	4.3 (6.4)	23.3 (21.7)	11.4 (20.5)	1
% daily non restorative sleep	21.7 (26.6)	9.1 (15.6)	28.2 (31.2)	12.4 (21.5)	46.1 (30.1)	10.4 (16.8)	1,2,3
5) Concentration problems							
CIS-concentration	14.9 (8.5)	8.9 (4.2)	18.6 (7.3)	13.5 (6.4)	16.9 (8.6)	8.6 (4.5)	1,2
SIP-alertness behaviour	105.0 (171.2)	9.4 (25.2)	151.1 (141.4)	61.5 (92.1)	156.6 (142.2)	47.8 (84.5)	1,2
RT1	0.33 (0.1)	0.31 (0.05)	0.34 (0.09)	0.34 (0.07)	0.33 (0.05)	0.35 (0.08)	
RT2	0.34 (0.05)	0.33 (0.04)	0.36 (0.08)	0.36 (0.06)	0.36 (0.05)	0.35 (0.04)	
RT3	0.49 (0.16)	0.42 (0.07)	0.46 (0.10)	0.5 (0.12)	0.44 (0.07)	0.44 (0.06)	3
MT1	0.27 (0.08)	0.23 (0.06)	0.29 (0.08)	0.31 (0.08)	0.26 (0.07)	0.28 (0.09)	1
MT2	0.34 (0.05)	0.33 (0.04)	0.36 (0.08)	0.36 (0.06)	0.35 (0.05)	0.35 (0.04)	1
MT3	0.49 (0.16)	0.42 (0.07)	0.46 (0.10)	0.50 (0.12)	0.44 (0.07)	0.44 (0.06)	1
Symbol Digit Test (SDT)	58.9 (10.2)	59.8 (11.3)	56.8 (15.9)	55.0 (11.7)	58.4 (9.6)	53.7 (10.9)	
6) Social functioning / social support							
SIP-social interaction	125.4 (158.5)	34.3 (68.2)	134.2 (156.1)	52.2 (111.8)	144.1 (191.0)	35.6 (110.7)	2
SSL-D	43.6 (10.9)	39.9 (5.9)	48.6 (10.3)	48.6 (11.9)	47.6 (11.4)	42.8 (12.8)	1
SSL-I	78.6 (18.0)	75.3 (12.5)	72.5 (10.7)	72.4 (14.7)	74.9 (12.2)	72.2 (12.4)	
SSL-N	10.5 (3.9)	8.7 (1.9)	11.3 (2.9)	9.7 (2.0)	10.2 (2.7)	9.7 (2.5)	2
7) Self-efficacy[1)]	19.7 (2.3)	21.2 (3.6)	16.7 (3.4)	19.2 (2.8)	17.8 (3.0)	20.9 (3.6)	1,2
8) Causal attribution[1)]							
Neuromuscular disorder	5.9 (1.3)	5.9 (1.6)	5.5 (1.3)	5.7 (0.8)	5.9 (1.3)	5.1 (2.0)	
Psychological	4.3 (1.2)	4.2 (1.6)	3.6 (1.1)	4.2 (1.2)	4.6 (1.4)	4.3 (1.5)	
9) Pain							
VAS (pain)	25.7 (25.3)	14.5 (17.6)	13.7 (20.0)	9.0 (15.9)	32.6 (25.9)	18.6 (21.6)	1,2
Daily observed pain (SOL)	3.8 (2.8)	2.0 (2.2)	1.7 (1.7)	1.2 (1.3)	4.2 (3.0)	2.2 (2.2)	1,2
III) Muscle strength							
MRC mean score	3.6 (0.83)	3.6 (0.89)	3.6 (0.84)	3.7 (0.92)	3.6 (0.86)	3.9 (0.92)	

Main effects: 1=group membership is significant, 2= fatigued vs. non-fatigued is significant. Interaction effect: 3= group x fatigue interaction effect is significant.

[1)] for FSHD n= 52, MD n=68, and HMSN n=60 (these questionnaires have not been filled out by those patients who reported that they never experience fatigue)

In all three groups, regression analyses showed that the model with the CIS-fatigue as dependent variable the dimension sleep disturbances (non restorative sleep) contributed significantly to fatigue severity. In FSHD also psychological distress (SCL-depression), and in HMSN patients concentration problems (SIP-alertness behaviour) contributed significantly to CIS-fatigue. In total, 32.5% of the fatigue severity subscale of the CIS was predicted in the FSHD group, 26.6% in the MD group and 53% in the HMSN group (Table 7.3a). Only in HMSN muscle strength (MRC) was included in the model but it did not contributed significantly.

In the analysis with the DOF as dependent variable only the dimension pain (VAS score) contributed significantly in FSHD patients, the dimension sleep disturbances (non restorative sleep) in MD patients, and the dimensions psychological distress (SCL-somatisation) and sleep disturbances (non restorative sleep) contributed significantly to the DOF score in HMSN patients. In total, 45.1% of the DOF score was predicted in the FSHD group, 25% in the MD group and 51.6% in the HMSN group (Table 7.3b). In none of the three neuromuscular disorders muscle strength (MRC) was included in the model.

TABLE 7.3a. Linear regression analysis to predict experienced fatigue (CIS-fatigue)

	Dependent variable CIS-fatigue					
	FSHD		**MD**		**HMSN**	
	Beta	Beta	Beta	p	Beta	p
Independent variables						
1) SIP-recreation and pastime	0.227	0.161	0.097	0.476	0.120	0.295
2) SIP-ambulation	0.063	0.623	-0.106	0.442	---	
3) SCL-depression	0.539	0.041	0.191	0.120	---	
4) non restorative sleep	0.272	0.026	0.298	0.007	0.321	0.003
5) SIP-alertness behaviour	-0.168	0.400	0.223	0.127	0.274	0.013
6) SIP-social functioning	-0.51	0.537	0.086	0.552	0.018	0.873
7) Self-efficacy	---		-0.149	0.246	---	
III) MRC	---		---		-0.206	0.061
Total R^2 (adjusted)	0.325		0.266		0.530	

Dimensions: 1) functional impairment in daily life; 2) physical activities; 3) psychological distress;
4) sleep disturbances; 5) concentration problems; 6) social functioning; 7) self-efficacy; III) disease severity.

Determinants of physiological fatigue (CAF and peripheral fatigue)

Regression analyses showed that with the CAF as dependent variable only pain (VAS score) contributed significantly in FSHD patients and none of the dimensions contributed significantly in HMSN patients. In total, 24% of the peripheral fatigue was predicted in the FSHD group and 15.5% in the HMSN group (Table 7.4a). In MD a model of contributing dimensions could not be developed, as none of the dimensions correlated significantly with the CAF.

The analysis with peripheral fatigue as dependent variable showed that only functional impairment in daily life (daily worked hours) contributed significantly in FSHD patients, sleep disturbances (daily general quality of sleep) and pain (daily observed pain) in MD patients, and only functional impairment in daily life (daily worked hours) contributed significantly in HMSN

patients. In total, 10.9% of the peripheral fatigue was predicted in the FSHD group, 13.3% in the MD group and 12.6% in the HMSN group (Table 7.4b).

TABLE 7.3b. Linear regression analysis to predict experienced fatigue (daily observed fatigue)

	Dependent variable CIS-fatigue					
	FSHD		**MD**		**HMSN**	
	Beta	p	Beta	p	Beta	p
Independent variables						
1) SIP-eating	0.159	0.192	---		0.172	0.072
1) SIP-body care and movement	---		-0.149	0.247	---	
2) SIP-mobility	---		-0.085	0.510	---	
3) SCL-anxiety	---		---		0.208	0.045
3) SCL-depression	---		0.152	0.139	---	
4) non restorative sleep	0.073	0.493	0.405	0.000	0.403	0.000
5) SIP-alertness behaviour	0.251	0.099	---		-0.027	0.773
6) SIP-social functioning	0.021	0.880	---		-0.017	0.864
6) SSL-I	---		0.126	0.214	---	
9) VAS (pain)	0.418	0.000	---		0.328	0.000
Total R^2 (adjusted)	0.451		0.250		0.516	

Dimensions: 1) functional impairment in daily life; 2) physical activities; 3) psychological distress; 4) sleep disturbances; 5) concentration problems; 6) social functioning; 9) pain.

TABLE 7.4a. Linear regression analysis to predict CAF

	Dependent variable CAF			
	FSHD		**HMSN**	
	Beta	p	Beta	p
Independent variables				
1) SIP-ambulation	---		0.215	0.098
3) SIP-emotional behaviour	0.114	0.344	---	
3) SCL-anxiety	---		0.239	0.129
4) SCL-sleep	---		0.175	0.269
9) daily observed pain (SOL)	0.476	0.000	---	
Total R^2 (adjusted)	0.242		0.155	

In MD patients, none of the dimensions were significant
Dimensions: 1) functional impairment in daily life; 3) psychological distress; 4) sleep disturbances; 9) pain.

TABLE 7.4b. Linear regression analysis to predict peripheral fatigue

	Dependent variable Peripheral fatigue					
	FSHD		**MD**		**HMSN**	
	Beta	p	Beta	P	Beta	p
Independent variables						
1) daily worked hours (SOL)	0.280	0.046	0.220	0.052	0.388	0.004
4) daily general quality of sleep (SOL)	0.009	0.947	0.253	0.029	-0.154	0.235
9) daily observed pain (SOL)	-0.185	0.193	0.247	0.032	-0.161	0.218
Total R^2 (adjusted)	0.109		0.133		0.126	

Dimensions: 1) functional impairment in daily life; 4) sleep disturbances; 9) pain.

DISCUSSION

As far as we know this is the first study in which both experienced fatigue and physiological fatigue were studied in three relatively common neuromuscular disorders.
This study showed that experienced fatigue is related to central activation failure (CAF), but not to peripheral fatigue in a large cohort of patients with FSHD, adult-onset MD, and HMSN type I. However, CAF explained only a small amount of the variance of experienced fatigue. There was no significant difference in CAF, peripheral fatigue or disease severity between patients with severely experienced fatigue and non-severely experienced fatigue. Experienced fatigue, CAF, and peripheral fatigue appeared to be separate types of fatigue. Although the respective determinants of experienced fatigue appear to be quite similar in the three neuromuscular disorders, the amount of explained variance differed considerably.
In the three neuromuscular disorders, severe experienced fatigued was associated with more symptoms on the various dimensions: more functional impairment in daily life, more psychological distress, more sleep disturbances, more concentration problems, less social functioning, and higher levels of pain.
In patients with MD, the severely fatigued patients have higher scores than the
non-severely fatigued patients of communication problems and these scores were significantly higher than in the two other patient groups. This difference is understandable by the disease-specific problems associated with a multisystem disorder like MD. Myotonic dystrophy often leads to nasal and dysarthic speech, which possibly causes communication difficulties (35).
As far as we know, the relation between experienced fatigue and actual physical activity (actimetry) in patients with neuromuscular disorders has not been investigated before. Patients with FSHD and HMSN with severe experienced fatigue appeared to have lower levels of actual physical activity. Thus, patients who are more fatigued move less, compared with patients without experienced fatigue. Whether fatigue is the cause or the result of the physical inactivity, and/or muscle weakness cannot be concluded from these cross-sectional data. Remarkably, in MD patients we found no difference in actual physical activity between severely fatigued and non-severely fatigued. This means that actual physical activity has no relationship with fatigue in this patient group.
Severely fatigued patients reported higher level of psychological distress than non-severely fatigued patients in all three groups. No significant differences were found between the three neuromuscular disorders on psychological distress. We cannot say whether distress is an antecedent or consequent of fatigue, because of the cross-sectional data.
In all three disorders, sleep disturbances showed an important relation with experienced fatigue. According to previous reports, sleep disturbances are very common in (chronic) neurological disorders (35). Various sleep disruptions may result from impaired motor functions, nocturnal pain and (muscle) cramps, restless legs and periodic limb movement disorders. These disruptions might lead to excessive daytime sleepiness and fatigue (36). HMSN patients reported significantly more sleep problems than the two other groups. Dematteis et al found an association between HMSN and sleep apnoea (37). Experienced fatigue is common to a wide range of sleep disorders and might leads to insomnia (37). Additional studies are needed to analyse the specific sleep disturbance in patients with neuromuscular disorders and the specific relation with fatigue.

We found a relation between concentration problems (SIP-alertness behaviour) and experienced fatigue in the three disorders. Pfeiffer et al showed that the statements of the SIP alertness behaviour ('I have minor accidents', or "I react slowly to things that are said or done") are statements which illustrate typical problems of patients with neuromuscular disorders, who behave clumsily and are slow in important activities (38).
In all three groups, severely fatigued patients reported more impairment in social interaction than non-severely fatigued patients. Severely fatigued patients had a lower sense of control with respect to their fatigue symptoms than non-severely fatigued patients. No differences were found between severely fatigued and non-severely fatigued patients of causal attribution. However, those patients who report that they never experience fatigue have not filled out the self-efficacy and causal attribution questionnaires. Finally, we found that patients with FSHD and HMSN turned out to report more often pain than MD patients. Pain is a significant problem for these disorders interrupting activities of daily living (39,40). The relationship between experienced fatigue and pain is weak.
We used two measurements for experienced fatigue as dependent variable: the CIS-fatigue, a general self-report measure, and the daily-observed fatigue (DOF) score. For both experienced fatigue measures about the same dimensions explained the variance in all tested models.

In this study physiological fatigue was divided in central activation failure, as measure of central fatigue, and peripheral fatigue. Determinants of the CAF were different for the three neuromuscular disorders and were different from the dimensions contributing to experienced fatigue. In FSHD patients CAF could be significantly explained by pain. This means that pain in FSHD has a great influence on the level of central activation. This was also found by Graven-Nielsen (41). In contrast, in HMSN none of the tested variables was significantly related to CAF explaining only a small amount of variance. In MD none of the variables of the dimensions could be put in the regression model.
There is a remarkable similarity in the three neuromuscular disorders in the variables that explained the variance of peripheral fatigue. Peripheral fatigue is defined as the ability of muscle to produce force declines during exercise. We found that daily worked hours, daily general quality of sleep and daily observed pain contributed to peripheral fatigue. However, these determinants explained only a small amount of the variance.
All determinants were measured with the self-observation list, filled out during two weeks after the experiment. Chaudhuri and Behan considered peripheral fatigue as a term for muscle fatigability due to disorders of muscle and neuromuscular junction (2). However, we found no relation between peripheral fatigue, muscle strength and disabilities.
Our data are cross-sectional, which affected the ability to make any definite conclusions about the cause and effect relationships between variables. Further work evaluating the causal pathways for the different types of fatigue and the role of determinants in moderating or mediating fatigue in patients with neuromuscular disorders is necessary. A longitudinal study of such factors might reveal which determinants can predict different types of fatigue.
In conclusion, results from this study indicate that fatigue in neuromuscular disorders should be distinguished in experienced fatigue and physiological fatigue (CAF and peripheral fatigue). Experienced fatigue is significantly but very modestly associated with central activation failure.

Experienced fatigue is not related with peripheral fatigue. The identification of different types of fatigue and the causally related determinants of the different types in these disorders can help us to develop specific interventions to reduce fatigue in patients with neuromuscular disorders.

REFERENCES

1. Krupp LB. Fatigue. Philadelphia: Butterworth Heinemann. 2003
2. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004; 363: 978-988.
3. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord 2001; 16: 190-196.
4. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology 1993; 43: 2016-2018.
5. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. Mov Disord 1999; 14: 237-241.
6. Werf van der S, van der Broek H, Anten H, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur J Neurol 2001; 45(1): 28-33
7. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
8. Stibrant Sunnerhagen K, Grimby G. Muscular effects in late polio. Acta Physiol Scand 2001; 1771: 335-340.
9. Paul RH, Cohen RA, Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
10. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune-mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
11. Kalkman JS, Schillings ML, van der Werf SP, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.
12. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
13. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
14. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients : a cross-sectional study. Ann of Oncol 2002 ; 13: 589-598.
15. Vries M de, Soetekouw PM, Meer van der JW, Bleijenberg G. Fatigue in Cambodia veterans. QJM 2000; 93: 283-289.
16. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001; 81: 1725-1789.
17. Kent-Braun JA. Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. Eur J Appl Physiol Occup Physiol 1999; 80: 57-63.
18. Schillings ML, Hoefsloot W, Stegeman DF, Zwarts MJ. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. Eur J Appl Physiol 2003; 90: 562-568.
19. Schillings ML, Kalkman JS, van der Werf SP, van Engelen BGM, Bleijenberg G, Zwarts MJ. Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. Clin Neurophysiol 2004; 115: 2518-2524.

20. Shield A, Zhou S. Assessing voluntary muscle activation with the twitch interpolation technique. Sports Med 2004; 34: 253-267.
21. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 157-170.
22. Vercoulen JH, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS) [The Checklist Individual Strength]. Gedragstherapie 1999; 32: 131-136.
23. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. The Sickness Impact Profile; results of an evaluation study of the Dutch version. Ned Tijdschr Geneeskd 1990; 134: 1950-1954.
24. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19: 787-805.
25. van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49: 373-379.
26. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
27. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behav Res Ther 1997; 35: 785-791.
28. Arindell WA, Ettema JHM. SCL-90, handleiding bij een multidimensionele psychopathologie-indicator. Swets & Zeilinger BV, Amsterdam 1986.
29. Houx PJ, Jolles J. Age-related decline of psychomotor speed: effects of age, brain health, sex, and education. Percept Mot Skills 1993; 76: 195-211.
30. Stinissen J, Willems PJ, Coetsier L, Hulsman WLL. Handleiding bij de Nederlandse bewerking van de WAIS. [Manual of the Dutch edition of the WAIS]. Amsterdam: Swets and Zeitlinger, 1970.
31. Van Sonderen E. Sociale Steun Lijst-Interacties (SSL-I) en Sociale Steun Lijst-Discrepanties (SSL-D). Noorderlijk Centrum voor Gezondheidsvraagstukken, Groningen, 1993.
32. Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, van der Wilt G, Spinhoven P, van der Meer JWM. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-847.
33. Medical Research Council. Aids to the examination of the peripheral nerve injuries. London: her Majesty's Stationery Office, 1981:1.
34. Emery AEH. Diagnostic criteria for neuromuscular disorders, 2nd edition. London: Royal Society of Medicine Press, 1997.
35. Shapiro CM, Devins GM, Hussain MRG. Sleep problems in patients with medical illness. Br Med J 1993; 306: 1532-1535.
36. Lichstein KL, Means MK, Noe SL, Aguillard RN. Fatigue and sleep disorders. Behav Res Ther 1997; 35(8): 733-740.
37. Dematteis M, Pépin JL, Jeanmart M, Deschaux C, Labarre-Vila A, Lévy P. Charcot-Marie-Tooth disease and sleep apnoe syndrome: a family study. The Lancet 2001; 357: 267-72.
38. Pfeiffer G, Wicklein EM, Ratusinski T, Schmitt L, Kunze K. Disability and quality of life in Charcot-Marie-Tooth disease type I. J Neurol Neurosurg Psychiatry 2001; 70: 548-550.
39. Bushby KM, Pollitt C, Johnson MA, Rogers MT, Chinnery PF. Muscle pain as a prominent feature of facioscapulohumeral dystrophy (FSHD): four illustrative case reports. Neuromuscl Disord 1998; 8: 574-579.
40. Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtree LD, Beardsley RM et al. Neuropathic pain in Charcot-Marie-Tooth disease. Arch Phys Med Rehabil 1998; 79: 1560-1564.
41. Graven-Nielsen T, Lund H, Arendt-Nielsen L, Danneskiold-Samsoe B, Bliddal H. Inhibition of maximal voluntary contraction force by experimental muscle pain: a centrally mediated mechanism. Muscle Nerve 2002; 26: 708-712.

CHAPTER 8

Pain and the relation with fatigue in patients with Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I

This chapter is submitted for publication as:
Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Pain and the relation with fatigue in patients with Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I.

ABSTRACT

Objectives

To determine the presence, localization and other characteristics of pain and its relation with fatigue in patients with relatively common types of neuromuscular disorders.

Methods

In total, 217 patients (65 Facioscapulohumeral Dystrophy, 79 adult-onset Myotonic Dystrophy and 73 Hereditary Motor and Sensory Neuropathy type I patients) were studied.

Pain was investigated with the McGill Pain Questionnaire, functional disability was measured with the Sickness Impact Profile, physical activity with an actometer, and muscle strength with the Medical Research Council (MRC) scale. Fatigue severity was assessed with the Checklist Individual Strength (CIS-fatigue).

Results

Pain complaints were reported by 77% of FSHD, 47% of MD, and 75% of HMSN patients. The main values of pain scores were significantly higher for the patients compared to a healthy reference group. The localization of pain is specific for each neuromuscular disorder. Pain was most frequently localized in body regions most affected by the neuromuscular disorder and localization thus differed between the three disorders. No significant difference were found in levels of functional disability, physical activity, and muscle strength between patients with and without pain in each neuromuscular disorder.

Conclusion

Pain is an important feature in the studied neuromuscular disorders and its distribution is related to the weakness and differs from fatigue in these disorders.

INTRODUCTION

Severe fatigue has been reported by the majority of patients with relatively common neuromuscular disorders (1). Clinical experience of our research group indicated that many patients with these disorders also report pain and consider it an important problem. Surprisingly, pain in neuromuscular disorders has received little attention: only a few studies have investigated pain complaints in patients with neuromuscular disorders (2-5).
The present study concerns three homogeneous populations of patients with relatively common, genetically well-defined neuromuscular disorders, namely: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; adult-onset myotonic dystrophy (MD), a multisystem disorder; and hereditary motor and sensory neuropathy type I (HMSN), a neurogenic disorder.
The first aim of the present study was to investigate the presence, the localization and other characteristics of pain in FSHD, MD, and HMSN and its relation with functional disability, physical activity, and muscle strength. The second aim was to examine the strength of the relationship between pain and fatigue in these disorders.

METHODS

Patients

Adult patients with a definite diagnosis of a neuromuscular disorder who could be classified into one of the following diagnostic categories were asked to participate: (1) facioscapulohumeral muscular dystrophy (FSHD), (2) adult-onset myotonic dystrophy (MD) or (3) hereditary motor and sensory neuropathy type I (HMSN-I). Patients are a subgroup of patients describes earlier (1). Written informed consent was obtained from all participating patients. The study was approved by the local ethics committee**.**

Pain

The McGill Pain Questionnaire (MPQ) was used for the assessment of different aspects of pain (6,7).The main outcome measure is the magnitude of pain at the current moment marked on the visual analogue scale (VAS): a score of 0 mm indicates no pain, and 100 mm indicates unbearable pain. During 12 days, patients filled pain complaints in a daily Self Observation List (SOL). Pain severity was rated four times a day on a scale of 0 (no pain) to 4 (severe pain). This daily observed pain (DOP) score could range from 0 to 16, and the twelve daily pain scores were averaged into one DOP score (8). The DOP score was compared with the scores of a reference group of 90 healthy people, consisting of 35 men and 55 women (mean age 37.1 years, sd 10.9), who participated as controls in previous studies at the Expert Centre Chronic Fatigue. Furthermore, four times a day patients were asked to mark in the SOL types of pain that applied best for that moment (muscle pain, joint pain, back pain, abdominal pain, headache, and sore throat) (8).

Functional disability

Functional disability was assessed using the Dutch version of the Sickness Impact Profile (SIP-12) (8,9). A higher score means more functional disability.

Physical activity
The level of physical activity was assessed using an actometer (Actilog V3.0), a device worn by the patients around the ankle for 12 consecutive days 10). During this period of 12 days the patients filled out the daily Self Observation List (SOL) (8).

Muscle strength
Muscle strength was determined using the Medical Research Council (MRC) grading scale (MRC; 0 to 5) investigating the strength of the shoulder abductors, grip force, foot extensors and knee extensors (11). These eight values (both left and right) were averaged.

Fatigue severity
Fatigue severity was assessed using a subscale of the Checklist Individual Strength (CIS*)* (13-15).

Statistics
Data analysis was performed using SPSS (version 12.0). Descriptive statistics were used for description of the sample. T-tests, chi-square, analyses of variance (ANOVA) with correction according to the Bonferroni multiple-comparison test and general linear model (GLM)-analyses were performed to test differences between groups. For comparison between patients with and without pain the Mann-Whitney test was used. Correlations were calculated with the Spearman coefficient (r) correlation. P values < 0.05 were regarded as statistically significant. In order to examine the contribution of the pain scores (DOP and VAS) to fatigue, linear regression analyses (enter-method) were performed.

TABLE 8.1. Pain characteristics of patients with pain of each neuromuscular disorder

	FSHD N=50 mean (sd)	**MD** N=37 mean (sd)	**HMSN-I** N=55 mean (sd)	p-value
MPQ:				
VAS-momentary pain	26.2 (22.1)	24.4 (19.8)	34.8 (22.8)	ns
Range VAS-momentary pain (0-100)	0 – 87	0 - 83	0 - 81	
Self Observation List:				
Daily Observed Pain (DOP)	3.6 (2.6) [b]	2.0 (1.8) [ac]	4.0 (2.8) [b]	0.001
Range DOP (0-16)	0 – 10.8	0 – 7.6	0 – 14.3	
% muscle pain	40.6 (38.8)	24.8 (33.3)	41.5 (37.8)	ns
% joint pain	21.6 (33.5)	8.2 (15.8) [c]	30.7 (35.4) [b]	0.003
% backache	22.5 (28.8)	13.5 (18.5) [c]	34.9 (39.0) [b]	0.005
% abdominal pain	2.3 (7.9)	3.5 (5.2)	4.6 (10.1)	ns
% headache	12.1 (23.0)	5.6 (10.5)	9.3 (17.2)	ns
% sore throat	5.7 (14.9)	1.0 (2.5)	2.6 (8.2)	ns

[a] Significantly different from FSHD, Bonferonni p<0.05
[b] Significantly different from MD, Bonferonni p<0.05
[c] Significantly different from HMSN, Bonferonni p<0.05

RESULTS

The patient sample consisted of 65 FSHD patients, 79 MD patients, and 73 HMSN patients. The mean (sd) age was 43.1 (10.3) in the FSHD group, 41.0 (9.9) in the MD group, and 42.4 (9.8) in the HMSN group. In the FSHD group 59% were female, in the MD group 56%, and in the HMSN group 41%. No significant differences were found in age, gender, marital status and level of education between the three groups.

Pain

Pain complaints were reported by 50 of the 65 FSHD patients (77%), by 37 of the 79 MD patients (47%), and by 55 of the 73 HMSN patients (75%)(Table 8.1).

Pain was present for more than 4 years in the majority of the patients (68% of the FSHD, 62% MD, and 55% HMSN patients). Pain had started gradually in 94% of the FSHD, 84% MD, and in 80% of the HMSN patients with pain. In 62% in FSHD, 81% MD, and 78% HMSN patients with pain the complaints were always localized in the same body regions. The localizations of pain indicated on the bodily outline of the MPQ are presented in Figure 1.

Frequently used adjectives to characterize the pain in all three groups were stabbing, nagging, stiff, and sore. Pain intensity was mostly described as mild to moderate.
Only 22% FSHD, 16% MD, and 20% HMSN patients used analgesics regularly.

The mean values of the daily-observed pain score were significantly higher for the patients (in FSHD 2.9, sd 2.6; in MD 1.5, sd 1.6; in HMSN 3.2, sd 2.9) compared to the healthy reference group (mean DOP 1.0, sd 1.3).

In none of the groups, we found significant differences in age, gender, QoL, physical activity, and muscle strength between patients with and without pain.

Relation between pain and fatigue

The severely fatigued FSHD and HMSN patients had significantly higher pain scores (DOP and VAS) than the non-severely fatigued patients. We found no differences in pain scores in the MD group.

With regression analyses we investigated the relation between CIS-fatigue (as dependent variable) and the pain scores (DOP and VAS) (as independent variables). In total, 16.4% of the experienced fatigue was predicted in the FSHD group, 3% in the MD group and 21.5% in the HMSN group.

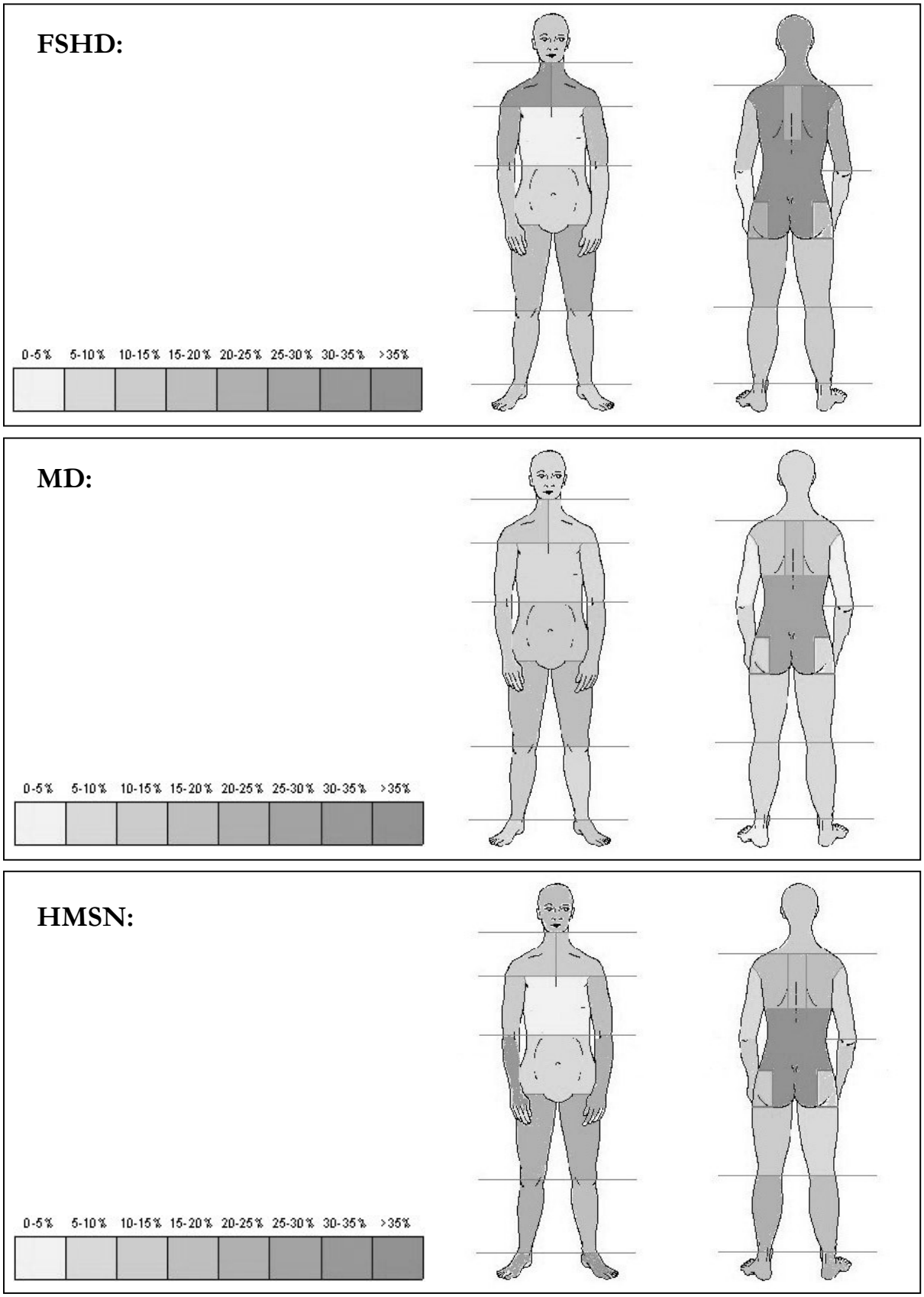

FIGURE 8.1. Localization of pain in front and back in each neuromuscular disorder (%)

DISCUSSION

This study shows that a high percentage of patients with homogeneous well-defined neuromuscular disorders report pain symptoms. About three quart of the FSHD and HMSN patients, and nearly half of the MD patients reported pain. Pain was most frequently localized in body regions generally known to be affected most by the neuromuscular disorder and thus localization differed between the three disorders. In none of the disorders was a statistically significant relationship between the presence of pain and age, gender, functional impairment, physical activity, or muscle strength.

In all three disorders, the Daily Observed Pain scores were higher than the scores of the reference group of 90 healthy people. This means that the reported pain is a clinically relevant phenomenon in these disorders.

Pain was most frequently localized in body regions mostly affected by the neuromuscular disorder and localization thus differed between the three disorders. Bushby attributed the pain in FSHD to postural problems in shoulders, hips and low back (2). Harper et al described that particularly back pain is often reported as a problem but was poorly studied in myotonic dystrophy so far (16). In HMSN patients, pain was most frequently present in lower back, feets and legs. This finding agreed with the clinical features of HMSN. In HMSN, muscle weakness and atrophy usually start in the foot and leg muscles. The rate of pain in HMSN patients is consistent with the findings of Carter et al (3).

In all three neuromuscular disorders we found a high presence of pain in the lower back. We know that back pain, especially pain in the lower back, is one of the most common health problems in adults.

Remarkable is the low consumptions of first-line analgesics in all three disorders. It may be possible that conventional first-line analgesics or anti-inflammatory therapy provide little effect in these patients. Or prescribing analgesics more frequently could be useful, further studies can give a definite answer.

In all three neuromuscular disorders pain appeared to be poorly related to fatigue. Severely fatigued FSHD and HMSN patients reported significantly more often pain than non-severely fatigued patients. We found no differences in pain between severely fatigued and non-severely fatigued MD patients.

Our study might have the following methodological limitations. Firstly, a selection bias is possible, because we only investigated ambulant patients. However, we have pain scores and experienced fatigue scores from 381 non-participating patients with neuromuscular disorders (74 FSHD, 243 MD, and 64 HMSN patients)(1). We found that the investigated group and the patients not included in this study did not differ in the levels of pain and fatigue. So it is unlikely that there is a systematic bias in our study. Secondly, the data were cross-sectional, which affected the ability to make any definite conclusions about the cause and effect relationships between variables. A longitudinal study of such variables might reveal which variables are causally related to pain and fatigue.

Awareness of pain and fatigue in these disorders is crucial to recognize important issues such as the impact on daily life, and the need for possibilities to reduce pain.

In conclusion, pain and fatigue are only poor related in FSHD and HMSN and unrelated in MD.

REFERENCES

1. Kalkman JS, Schillings ML, van der Werf SP, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.
2. Bushby KMD, Pollitt C, Johnson MA, Rogers MT, Chinnery PF. Muscle pain as a prominent feature of facioscapulohumeral muscular dystrophy (FSHD): four illustrative case reports. Neuromusc Disord 1998; 8: 574-579.
3. Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtee LD, Beardsley RM, Abresch RT, Bird TD. Neuropathic pain in Charcot-Marie-Tooth Disease. Arch Phys Med Rehabil 1998; 79: 1560-1564.
4. Abresch RT, Carter GT, Jensen MP, Kilmer DD. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. Am J Hosp Palliat Care 2002; 19: 39-48.
5. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975; 1: 277-299.
6. Van der Kloot WA, Oostendorp RA, van der Meij J, van den Heuvel J. [The Dutch version of the McGill Pain Questionnaire: a reliable pain questionnaire]. Ned Tijdschr Geneeskd. 1995; 139(13): 669-673.
7. Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, van der Wilt G, Spinhoven P, van der Meer JWM. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-847.
8. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19(8): 787-805.
9. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. The sickness impact profile; results of an evaluation study of the Dutch version. Ned Tijdschr Geneeskd 1990; 134.40: 1950-1954.
10. van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49.5: 373-379.
11. Medical Research Council. Aids to the examination of the peripheral nerve injuries. London: her Majesty's Stationery Office, 1981:1.
12. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
13. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 157-170.
14. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649
15. Harper PS, van Engelen BGM, Eymard B, Wilcox DE. Myotonic dystrophy: present management, future therapy. New York: Oxford University Press, 2004.

CHAPTER 9

Influence of relatives on fatigue experienced by patients with Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I

This chapter was published as:
Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Influence of relatives on fatigue experienced by patients with Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I.
European Neurology, 2006; 56: 24-30.

ABSTRACT

Objectives

Experienced fatigue is a common symptom experienced by patients with various neuromuscular disorders. The purpose of this study was to assess the influence of relatives on fatigue experienced by patients with various neuromuscular disorders.

Methods

In total, 106 close relatives of patients with Facioscapulohumeral Dystrophy (FSHD), adult-onset Myotonic Dystrophy (MD), and Hereditary Motor and Sensory Neuropathy type I (HMSN), completed the Checklist Individual Strength (CIS) for themselves, and how they thought their relatives filled in this questionnaire. We studied at the agreement between the two. The reaction of the relative to the fatigue and to the neuromuscular disorder of the patient was assessed by the Family Response Questionnaire. Marital dissatisfaction was also measured. The influence of the relative's response to the patients' fatigue and the relatives' fatigue on the fatigue of the patient was tested in linear regression models.

Results

In all three patient groups, the responses of the relatives to fatigue and disease were characterized by sympathetic-empathic responses. Low agreement existed between relatives and MD patients ($r=0.26$) over the patients' level of fatigue but higher agreement between relatives and FSHD ($r=0.67$) and HMSN ($r=0.73$) patients. The spouses of MD patients reported less marital satisfaction. The sympathetic-empathic responses of relatives of FSHD and HMSN patients, and in FSHD also fatigue experienced by the relative, contributed significantly to higher levels of fatigue experienced by the patients.

Conclusion

The sympathetic-empathic responses of close relatives to the fatigue of the patient were related to higher levels of fatigue experienced by FSHD and HMSN patients, but not in MD patients.

INTRODUCTION

Fatigue is a symptom experienced by the majority of patients with relatively common neuromuscular disorders (1). Fatigue can have a major impact on patients' functioning and activities of daily living, and on psychological well being (1-4). The effects are not limited to the patient, the relatives of the patient can suffer as well (5).
It is known that chronic diseases might also affect the quality of life of close relatives (6-7). Close relatives can provide emotional and instrumental support to the disabled individual in order to help the patient cope with the disease. Relatives are also able to reinforce their partners to engage in activities in daily life (5). Especially in chronic diseases, the major burden of care falls on the spouse and other close family members (8). To our knowledge, there has been no study to date that has asked the relatives of patients with neuromuscular disorders about their own level of fatigue and neuromuscular disorder of the patient.
Therefore, we conducted a study of patients and their spouses or close relatives in three genetically well-defined neuromuscular disorders: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; myotonic dystrophy (MD), a multisystem disorder; and hereditary motor and sensory neuropathy type Ia (HMSN), a neurogenic disorder.
The purpose of this study was three-fold: 1) to investigate the level of fatigue experienced by the close relatives and their responses to the fatigue and the neuromuscular disorder of the patient, 2) to determine if the close relatives are able to correctly perceive the level of fatigue experienced by the patient, and 3) to determine the influence of the relatives' responses and level of fatigue on the level of fatigue experienced by the patient.

METHODS

Patients and close relatives

Adult patients with a definite diagnosis of a neuromuscular disorder who could be classified into one of the following three diagnostic categories were asked to participate: (1) facioscapulohumeral muscular dystrophy (FSHD), (2) adult-onset myotonic dystrophy (MD) or (3) hereditary motor and sensory neuropathy type I (HMSN-I). They were recruited from the outpatient clinic of the Neuromuscular Centre, based at the Institute of Neurology of the Radboud University Nijmegen Medical Centre, and from the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland, VSN).
In total, 134 patients were asked for a permission to send a booklet with questionnaires, to their closest relative (spouse, parent or other). Written informed consent was obtained from all participating patients and their close relatives. The regional ethics committee approved the study.

Experienced fatigue

The Checklist Individual Strength (CIS*)* is a 20-item questionnaire and measures the following four aspects of fatigue during the previous two 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 high levels of fatigue, high levels of concentration problems, low motivation and low levels of physical activity (9,10). CIS-fatigue score equal or higher 35 was used to identify severe fatigue (11).
The CIS was used to assess the fatigue experienced by both the patients and the relatives. The CIS-fatigue scores of the relatives were compared with the scores of a reference group of 78 healthy controls (mean age healthy controls 48.1, sd 6.2) who participated as controls in previous studies at the Expert Centre Chronic Fatigue (12).

Experienced fatigue relative over patient
For use by relatives, the Checklist Individual Strength was rephrased to refer to the patient and called Checklist Individual Strength relative over patient (CIS-rop).

Family response
The Family Response Questionnaire (FRQ) contained 25 questions and scored on four dimensions: sympathetic and empathic responses (7 items, range 7-35), active engagement (5 items, range 5-25), rejecting and hostile responses (7 items, range 7-35), and concern with self (6 items, range 6-30) (13). Each item was scored on a 5-point Likert scale.
Sympathetic-empathic responses imply trying to imagine what the patient feels like, making positive supportive statements. Active engagement is trying to find out more about the symptom or illness by reading, discussing with the patient. Rejecting or hostile responses were disbelieving the patient's complaints or minimizing them. Concern with self means that relatives are concerned with the effect of the patient's illness on his/her own life, e.g., resents having to take on extra tasks.
A higher score indicates more of that response. In this study we used the FRQ for fatigue (FRQ-f) and the FRQ for neuromuscular disorder (FRQ-nmd). In the FRQ-f all questions are referring to fatigue of the patient and in the FRQ-nmd the same questions are referring to the neuromuscular disorder.

Marital satisfaction
The subscale marital satisfaction of the Maudsley Marital Questionnaire (MMQ) was used as a measure of marital quality (14-15). This scale marital satisfaction contains 10 questions on a 9-point Likert scale (range 0-80), with a higher score indicating more problems in the relation or lower marital satisfaction.

Statistics
Data analysis was performed using SPSS (version 12.0). Descriptive statistics were used for description of the sample. T-tests, chi-square, analyses of variance (ANOVA) with correction according to Bonferroni multiple-comparison test and general linear model (GLM)-general factorial were performed to test differences between groups. We used a Wilcoxon's t-test for dependent samples to compare the relatives over patients and patient's fatigue scores. P values < 0.05 were regarded as statistically significant. Correlations were calculated with the Spearman correlation coefficient (r). Furthermore, regression analyses were performed to examine the relationship between responses of the relative and the level of fatigue experienced by the relative

self to the level of fatigue experienced by of the patients. The dependent variable was the CIS-fatigue score of the patient, and the independent variables were the responses of the close relative and the CIS-fatigue score of the relative.

RESULTS

Patient-relative couples

From the 112 close relatives (84%) who returned the questionnaires, 6 relatives were excluded because they did not complete the questionnaire booklet..

One hundred and six relative and patient couples participated in this study (33 couples of FSHD patients, 32 of MD patients and 41 couples of HMSN patients). Demographic characteristics of the three groups of relatives are listed in Table 9.1. No significant differences were found in age and sex between the groups. In the MD couples, the percentage of spouses is the lowest of the three groups.

TABLE 9.1. Demographic characteristics of relatives of patient with three types of neuromuscular disorders

	Relatives of FSHD N=33	**Relatives of MD N=32**	**Relatives of HMSN N=41**
Age	46.7 (9.7)	48.5 (10.7)	46.7 (13.2)
M/F (%)	36% / 64%	34% / 66%	44% / 56%
Relation of patient (N)			
Spouse	31	19	31
Years of living together	21.0 (10.4)	21.8 (11.3)	18.1 (12.0)
Mother/father		7	4
Sister/brother		2	1
Daughter/son	1		2
Good friend	1	4	3

TABLE 9.2. Demographic characteristics of patients with three types of neuromuscular disorders

	FSHD patients N=33	**MD patients N=32**	**HMSN patients N=41**
Age	48.9 (13.7)	41.8 (9.5)	43.7 (10.7)
M/F (%)	61% / 39%	56% / 44%	42% / 58%
Marital status			
married/living together	31	19	31
divorced		2	2
widowed	1		
living independently	1	6	5
living with parents		5	2
Higher education (>= 12 years)	9 (27%)	7 (22%)	11 (27%)
Employment (paid job)	23 (70 %)	23 (72%)	28 (69%)
CIS-fatigue	33.5 (12.2)	37.7 (10.8)	33.6 (12.6)

Table 9.2 shows the demographic characteristics of the patients. No significant differences were found in age, sex, level of education, and employment between the three neuromuscular disorders. We found no differences in age between relatives and patients.
Patients dropped out mostly because they did not have a partner (n=17). The patients who refused to take part in this study did not differ from the participating subjects with regard to age, gender, marital status, level of education, employment status, and fatigue severity.

Experienced fatigue and family responses of relatives

There was no difference between the relatives of the different patient groups with regard to the fatigue they experienced. Eighteen % of the relatives of FSHD patients experienced severe fatigue (CIS-fatigue >=35), 16% of the relatives of the MD patients, and 22% of the family members of the HMSN patients (Table 9.3). The mean value for CIS-fatigue was higher for the relatives than for the healthy reference group (mean healthy controls 19.4, sd 11.0).

TABLE 9. 3. Experienced fatigue and responses to fatigue and neuromuscular disorder of relatives of patients with three types of neuromuscular disorders

	Relatives of FSHD N=33	Relatives of MD N=32	Relatives of HMSN N=41	p-value
CIS-relatives				
CIS-fatigue	22.6 (11.3)	22.8 (12.3)	25.1 (12.9)	ns
CIS-concentration	11.8 (6.8)	12.7 (6.7)	10.3 (5.3)	ns
CIS-motivation	9.7 (4.5)	11.3 (5.9)	9.79 (4.5)	ns
CIS-activity	5.9 (2.9)	5.9 (3.0)	6.7 (4.6)	ns
FRQ-fatigue				
FRQ-f-sympathetic -empathic	16.8 (4.4)	17.8 (4.5) [c]	15.2 (3.5) [b]	ns
FRQ-f-active engagement	9.5 (2.4)	10.3 (3.4) [c]	8.4 (2.0) [b]	ns
FRQ-f-rejecting-hostile	9.1 (2.2)	9.6 (2.3)	8.8 (2.1)	ns
FRQ-f-concern with self	8.5 (2.5)	9.3 (3.9) [c]	7.2 (1.7) [b]	0.006
FRQ-neuromuscular disorder				
FRQ-nmd-sympathetic -empathic	16.9 (4.1)	17.6 (4.5)	15.7 (3.8)	ns
FRQ-nmd-active engagement	10.5 (3.1)	10.4 (3.2)	9.2 (2.7)	ns
FRQ-nmd-rejecting-hostile	8.7 (1.8)	9.4 (2.2)	8.7 (2.1)	ns
FRQ-nmd-concern with self	8.4 (2.4) [c]	9.2 (2.9) [c]	6.7 (1.4) [ab]	0.000

[a] Significantly different from relatives of FSHD patients, Bonferonni p<0.05
[b] Significantly different from relatives of MD patients, Bonferonni p<0.05
[c] Significantly different from relatives of HMSN patients, Bonferonni p<0.05

In all three patient groups family responses were characterized by sympathetic-empathic responses. We found no differences in responses to fatigue and to the neuromuscular disorder. The relatives of HMSN patients had the lowest scores on the subscale "concern with self". (Table 9.3). The subscales of the FRQ-fatigue were strongly correlated to the subscales of the FRQ-neuromuscular disorder (range r=0.76 to r=0.91).

Agreement of experienced fatigue and marital satisfaction

In MD couples no significant correlation between patients fatigue and the perception of patients' fatigue by the relative was found (Table 9.4). In FSHD and HMSN couples high and significant correlation was found between patients' fatigue and the perception of patients fatigue by the relative. In HMSN couples no correlation was found between patients reduced concentration and the perception of the relative.

The relatives of the MD patients reported lower marital satisfaction than the other relatives, and there was lower agreement in marital satisfaction of the MD couples than the two other groups.

TABLE 9.4. Correlations between relatives over patients and patient's experienced fatigue of three types of neuromuscular disorders and in couples who lived together the marital satisfaction.

	Relative over patient (CIS-rop)				
	CIS-rop-fatigue	CIS-rop-concentration	CIS-rop-motivation	CIS-rop-activity	MMQ-marital satisfaction
Patients:					
CIS-fatigue					
FSHD	0.627**				
MD	0.260				
HMSN	0.728**				
CIS-concentration					
FSHD		0.409*			
MD		0.432*			
HMSN		0.230			
CIS-motivation					
FSHD			0.635**		
MD			0.409*		
HMSN			0.437**		
CIS-activity					
FSHD				0.653**	
MD				0.490*	
HMSN				0.439**	
MMQ-marital satisfaction 1)					
FSHD					0.765**
MD					0.402*
HMSN					0.814**

* correlation is significant at the 0.05 level (2-tailed) **correlation is significant at the 0.01 level (2-tailed)

1) MMQ-marital satisfaction was only filled out by couples who lived together (31 FSHD couples, 19 MD couples, HMSN 31 couples)

Influence of the response and the level of experienced fatigue of relatives to patients' fatigue

Regression analyses showed that sympathetic-empathic responses (FRQ-f) of the relatives contributed significantly to the level of fatigue experienced by the patient in FSHD and HMSN couples. In the FSHD couples also the level of fatigue by the relative himself contributed significantly. In the MD couples, none of the various responses of the relatives contributed significantly to the level of fatigue experienced by the patients (Table 9.5).

TABLE 9.5. Linear regression analyis to predict experienced fatigue of the patient of each neuromuscular disorder

	Dependent variable CIS-fatigue of the patient					
	FSHD		**MD**		**HMSN**	
Relatives	Beta	p	Beta	p	Beta	p
FRQ-f-sympathetic-empathic	0.461	0.025	0.058	0.822	0.467	0.021
FRQ-f-active engagement	-0.073	0.725	0.374	0.207	-0.142	0.468
FRQ-f-rejecting-hostile	-0.155	0.339	0.067	0.775	-0.291	0.287
FRQ-f-concern with self	0.288	0.132	-0.227	0.399	0.229	0.423
CIS-fatigue of the relative	-0.480	0.008	-0.133	0.575	0.175	0.308
Total R^2 (adjusted)	0.384		0.064		0.120	

DISCUSSION

As far as we know this is the first study in which the responses of close relatives to patients' experienced fatigue and disease were studied in neuromuscular disorders. Most studies of close relatives are focussed on caregivers of patients with cancer, Alzheimer's disease and Parkinson's disease (8,16-17). These studies showed that spouses and other relatives commonly respond in an unsupportive manner. As a relative becomes increasingly disabled by the patients' disease, the role of the significant other is altered, and the relative may be required to relinquish social, leisure, and family activities outside the home, as well as restrict time on their own, in order to assist in the medical care and household responsibilities. Studies have shown that the greater the disability imposed by an illness, the more likely significant others are to respond negatively (8,17). In this study we investigated relatives of patients with slowly progressive neuromuscular disorders.

The mean fatigue severity of the relatives was significantly higher compared to the scores of a reference group of healthy controls. We found no differences in the severity of fatigue experienced by the relatives of patients with various neuromuscular disorders. Although the patients in this study were mildly affected by their disorder, one could see the heightened level of fatigue experienced by the close relatives in relation to or as a burden of the disease of their partner. It is possible that the heightened fatigue of the relatives is caused by the disease and/or fatigue of the partner. Probably, the relatives were not fulltime caregivers of the patients in this study because all patients were ambulant and in all three groups more than 69% of the patients were employed. On the other hand, we know that at least about half of the patients suffer from severe fatigue, resulting in impairment in several domains. Therefore, some care will be given by the relative. However, we do not have specific information of the health status of the relatives, we do not know the influence of the health status on fatigue.

The responses of the relatives to both the fatigue and neuromuscular disorder of the patients were mainly sympathetic-empathic responses and similar within relatives of patients with the various disorders. The relatives reported that they were trying to imagine what the patient feels,

making positive supportive statements. Relatives of MD patients reported the highest score on the subscale 'concern with self' of the Family Response Questionnaire. The relatives were concerned about the effect of the patients' disease on their own life, e.g., resented taking on extra tasks. Besides, the relatives of MD patients reported the highest marital dissatisfaction. An explanation could be that the MD patient may not understand the impact of his/her disorder on the life of the relative, and/or the relative is frustrated about the practical limitations of the disorder. We found a lower percentage of MD patients living with a partner than in the other two groups. This was also found in another study (20).

Overall, the relatives rated the level of fatigue experienced by the patient lower than the patient did himself. The least agreement was found in MD couples. In spouses living together we found more disagreement in marital satisfaction within MD couples than within FSHD and HMSN couples. Possibly, disease-specific problems associated with a multisystem disorder like MD, such as apathy, lack of expressiveness, and inability to anticipate pleasure, contribute to more marital dissatisfaction (18-19). We found that relatives of patients with MD had difficulty in estimating the level of fatigue experienced by the patient. The same reaction can be supposed for the doctors of patients with MD and may influence their relationship.

We found that the responses of the relatives led to higher levels of fatigue experienced by the patients in FSHD and HMSN couples. In FSHD couples also the level of fatigue experienced by the relative contributed to the level of fatigue in the patient. Receiving higher levels of sympathetic support from the relatives, such as getting help, was associated with higher reports of fatigue in patients with FSHD and HMSN. The sympathetic-empathic responses were reinforcing the fatigue of the patient.

This study has some methodological limitations. Firstly, the data were cross-sectional, which affected our ability to make any definite conclusions about the cause and effect relationships between variables. Secondly, a selection bias is possible, because we only investigated ambulant patients. Thirdly, the patients were asked for a permission to send questionnaires to their closest relative. Patients dropped out mostly for the reason of not have a partner. In this study we found that the fatigue scores of patients with a spouse did not differ from those of the patients with another relative. However, we don't know whether the relatives of the non-investigated group are different in their reaction to the patient from the relatives in this study.

To date, there is very little information about the impact of patients with slowly progressive neuromuscular disorders on close relatives. This study reveals that a chronic neuromuscular disorder can have an effect on close relatives and vice versa. Especially the responses of close relatives influenced the level of fatigue experienced by the patient.

One important point in clinical practice for the doctor of patients with neuromuscular disorders is to try to identify relatives who are at high risk of burden by their partner' disease. Furthermore, these findings emphasise the importance that not only the patient, but also the relative should be target of information, this meaning that the close relative should also visit the physician together with the patient in order to reduce and manage the consequences of the disorder in both.

REFERENCES

1. Kalkman JS, Schillings ML, van der Werf SP, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.
2. Paul RH, Cohen RA Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
3. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
4. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune-mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
5. Krupp LB. Fatigue. Philadelphia: Butterworth Heinemann. 2003.
6. Carter JH, Stewart BJ, Archbold PG, Inoue I, Jaglin J, Lannon M et al. Living with a person who has Parkinson's disease: The spouse's perspective by stage of disease. Mov Disord 1998; 13: 20-28.
7. Schwartz L, Kraft GH. The role of spouse responses to disability and family environment in multiple sclerosis. Am J Phys Med Rehabil 1999; 78: 525-532.
8. Secker DL, Brown RG. Cognitive behavioural therapy (CBT) for carers of patients with Parkinson's diseae: a preliminary randomised controlled trial. J Neurol Neurosurg Psychiatry 2005; 76: 491-497.
9. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
10. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 57-170.
11. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
12. Servaes P,Verhagen C, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients, a cross-sectional study. Ann Onco 2002; 13: 589-598.
13. Cordingley L, Wearden A, Appleby L, Fisher L. The family response questionnaire: A new scale to assess the responses of family members to people with chronic fatigue syndrome. J Psychosom Res 2001; 51: 417-424.
14. Arrindell WA, Schaap C. The Maudsley Marital Questionnaire (MMQ): An extension of its construct validity. Br J Psychiatry 1985; 147: 295-299.
15. Arrindell WA, Boelens W, Lambert H. On the psychometric properties of the Maudsley Marital Questionnaire (MMQ): Evaluation of self-ratings in distressed and 'normal' volunteer couples based on the Dutch version. Person Individ Diff 1983; 4: 293-306.
16. Clipp EC, George LK. Patients with cancer and their spouse caregivers. Cancer 1992; 69: 1074-1079.
17. Thommessen B, Aarslund D, Braekhus A, Oksengaard AR, Engedal K, Laake K. The psychosocial burden on spouses of the elderly with stroke, dementia and Parkinson's disease. Int J Geriatr Psychiatry 2002; 17: 78-84.
18. Bungener C, Jouvent R, Delaporte C. Psychopathological and emotional deficits in myotonic dystrophy. J Neurol Neurosurg Psychiatry 1998; 65: 353-356.
19. Harper PS, van Engelen BGM, Eymard B, Wilcox DE. Myotonic dystrophy: present management, future therapy. New York: Oxford University Press, 2004.
20. Perron M, Veillette S, Mathieu J. Myotonic dystrophy. 1. Socio-economic and home-environment characteristics of the patient. Can J Neurol Sci 1989; 16: 109-113.

CHAPTER 10

The development of a model of fatigue in neuromuscular disorders: a longitudinal study

This chapter is submitted for publication as:
Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G.
The development of a model of fatigue in neuromuscular disorders: a longitudinal study.

ABSTRACT

Background

Severe fatigue is reported by the majority of patients with three relatively common types of neuromuscular disorders.

Objective

To identify predictors of fatigue in a longitudinal study and to develop a model of experienced fatigue in patients with three neuromuscular disorders.

Methods

198 patients (60 Facioscapulohumeral Dystrophy (FSHD), 70 adult-onset Myotonic Dystrophy (MD) and 68 Hereditary Motor and Sensory Neuropathy type I (HMSN) patients) were studied twice during an 18-months period. Fatigue severity was assessed with the Checklist Individual Strength (CIS-fatigue). A multidimensional assessment method was used including self-report questionnaires, a daily Self Observation List, and a measure of physical activity (actometer). Muscle strength was determined using the Medical Research Council (MRC) scale. Structural equation modelling was used to develop and test a model of factors contributing to the persistence of experienced fatigue.

Results

Muscle strength, self-reported physical activity, sleep disturbances and pain at baseline contributed directly or indirectly to experienced fatigue and impairment at follow-up. Lower muscle strength contributed to lower levels of physical activity, which in turn contributed to experienced fatigue severity. The model showed excellent fit for the whole group of neuromuscular disorders. In FSHD, also pain contributed to physical activity. A model with the actometer as measurement for actual physical activity in stead of self-report showed an excellent model fit in FSHD and HMSN, but an insufficient fit in MD.

Conclusion

The model of perpetuating factors for fatigue in FSHD and HMSN is different from the model in MD. The main difference is in physical (in)activity. These differences have implications for interventions based on these models.

INTRODUCTION

Neuromuscular disorders include a variety of conditions that affect the peripheral nervous system (1,2). The peripheral nervous system includes peripheral nerves, the motor-nerve cells in the spinal cord, and the nerve-muscle (neuromuscular) junction. There are different types of neuromuscular disorders. Despite the many different neuromuscular disorders, only a limited number of symptoms occur: muscle weakness is the most typical.

This study concerns three genetically well defined, homogeneous, and large populations of patients with relatively common neuromuscular disorders, namely facioscapulohumeral muscular dystrophy (FSHD), adult-onset myotonic dystrophy (MD) and hereditary motor and sensory neuropathy type I (HMSN). FSHD is an autosomal dominantly inherited myopathy, initially characterized by weakness and atrophy in facial, upper arm, and shoulder girdle muscles often progressing to affect peroneal and pelvic girdle muscles (3).

MD is the most common form of muscular dystrophy and is also an autosomal dominant hereditary multisystemic disease characterized by myotonia, muscle weakness and atrophy, cataracts, cardiac abnormalities, excessive daytime sleepiness, and disorders of other systems such as the endocrine system, gastrointestinal tract, skin and bone (4). HMSN, also known as Charcot-Marie-Tooth disease, forms a heterogeneous group of slowly progressive heritable disorders of the peripheral nervous system (5).The most common form is type I. The clinical features of HMSN type I include a symmetrical distal muscle weakness and atrophy, and areflexia and sensory impairment with distal loss of touch, pain, vibration and joint position sense. Thus, this study compares patients with three different neuromuscular disorders, including a myopathy, a multisystem disorder and a neuropathy.

Fatigue is a common symptom of various neurological disorders and is mostly studied in multiple sclerosis, Parkinson's disease, after stroke but less in neuromuscular disorders (6-11). Within the group of neuromuscular disorders, fatigue has mostly been described in patients with post-poliomyelitis syndrome, myasthenia gravis, and immune mediated neuropathies like Guillain-Barré syndrome (12-15). In a previous cross-sectional study we concluded that severe fatigue was a complaint in more than 60% of a large sample of patients with relatively common neuromuscular disorders like FSHD, adult-onset MD and HMSN-I (16). In addition, severe fatigue appeared to be related to functional impairment in daily life.

Until now, no longitudinal studies have been performed in which fatigue is examined in patients with neuromuscular disorders. Therefore it is not known which factors prospectively predict the level of fatigue.

Our research group has developed a multidimensional assessment method to determine fatigue in several chronic disorders (17-20). This multidimensional assessment method identifies various dimensions relevant for fatigue: functional impairment in daily life, physical activity, psychological distress, sleep disturbances, concentration problems, social functioning, social support, self-efficacy, and causal attribution. In chronic disorders like neuromuscular disorders also pain and muscle strength are assessed.

This study presents the longitudinal data of a cohort of patients with three different neuromuscular disorders during an 18-month period. Furthermore, we develop a longitudinal model to predict fatigue. Based on relations between baseline variables at follow-up, we will

formulate a model of predicting factors of fatigue. This model is possible by using the statistical technique "structural equation modelling", also referred to as "causal modelling". This technique makes it not only possible to test different relationships simultaneously but also to compare the data fit of two or more proposed models. Such a model can be a basis for treatment interventions for fatigue. Therefore, the aim of this study is (1) to identify factors that predict fatigue in various neuromuscular disorders, and (2) to develop a model of factors contributing to the persistence of fatigue in these disorders.

METHODS

Patients

Adult patients in the age of 18 to 60 years with a definite diagnosis of a neuromuscular disorder who could be classified into one of the following three diagnostic categories were asked to participate: (1) facioscapulohumeral muscular dystrophy (FSHD), (2) adult-onset myotonic dystrophy (MD) or (3) hereditary motor and sensory neuropathy type I (HMSN). Patients were recruited from the outpatient clinic of the Neuromuscular Centre of the Radboud University Medical Centre and form the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland). Patients are a subgroup of patients described earlier (16).

Only ambulatory patients were included. From the 527 patients that were eligible 331 patients were willing to participate in the research project. We invited 240 patients (for each neuromuscular disorder at least 70 patients) and 217 patients (65 FSHD, 79 MD, and 73 HMSN patients) complete data could be collected. Patients dropped out (n=23) for several reasons: high travel distance, inability to take a day off or personal reasons. Written informed consent was obtained from all participating patients. The following demographic features were collected: age, gender, marital status, and highest level of education and current status of employment. The regional ethics committee approved the study.

Procedure

The patients who agreed to take part in the study were invited to the Radboud University Nijmegen Medical Centre for the assessments. Within the multidimensional assessment method different modalities of assessment were used. These include self-report questionnaires,
standardised sleep- and complaint diaries, neuropsychological tests, and actography (actometer).

On the first day patients endure a physical examination including the MRC grading scale. The day after the patients start with the daily Self Observation List (SOL) during a period of 12 complete days. During this period the patients were wearing an actometer. After this 12-day period, patients filled out several computerised questionnaires and neuropsychological tests. At baseline and at 18-month follow-up, the same dimensions were used again.

Dependent variables

Fatigue

The Checklist Individual Strength (CIS) is a 20-item questionnaire and measures the following four aspects of fatigue during the previous two 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, low motivation and low levels of activity (17,18,21). A CIS-fatigue score equal or higher 35 was used to identify severe fatigue (17).

Functional Impairment

The Sickness Impact Profile (SIP) was used to assess functional impairment. We used a sum score of the following subscales: body care and movement, home management, communication, work limitations, recreation and pastimes, and impairments with eating (22-23). Higher score indicate a higher level of functional impairment.

Independent variables

Physical activity

Two self-report measurements, the subscales mobility and ambulation of the Sickness Impact Profile, were used to assess physical activity.

The level of actual physical activity was assessed using an actometer (Actilog V3.0), a device worn by the patients around the ankle for 12 consecutive days (24). The actometer measures the number of accelerations over each 5-minute period. A general physical activity score is calculated by averaging the number of accelerations over the 12-day period (24).

Psychological distress

Psychological distress was measured with two self-report questionnaires: the Beck Depression Inventory for primary care (BDI-pc), and the Symptom Checklist-90 (SCL-90). The BDI-pc was used instead of the complete BDI, in order to prevent an overlap between physical aspects of fatigue with the somatic symptoms of depression (25,26). This shortened version of the BDI has 7 items and consists of cognitive and affective symptoms. A score of 4 or more is indicative of clinical depression. We also used the subscales anxiety and depression of the SCL-90 (27). Higher SCL-subscale scores indicate more distress.

Sleep disturbances

Self-report sleep disturbances (e.g., light and fragmented sleep, difficulties with sleep initiating) were measured with the sleep subscale of the SCL-90 (27). In a dairy, the Self Observation List, patients reported perceived sleep disturbances every day (daily general quality of sleep, unrestorative sleep, hours of sleep during 24-hours, wake-up time and bed time) (28). Total scores range from 0 to 100. Higher score indicates higher daily sleep disturbances.

Neuropsychological impairment
Self-reported concentration problems were measured with the concentration subscale of the CIS and the alertness behaviour subscale of the SIP. In order not to rely only on self-report data we used neuropsychological tests. The Complex Reaction Time (CRT) Task measures the speed of information processing and is comprised of three successive tasks, each providing a reaction time (RT1, RT2, RT3) and movement time (MT1, MT2, MT3) (29). RT reflects speed of information processing and MT reflects motor speed. The Symbol Digit subtest (SDT) of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) assesses the ability to concentrate, and consists of pairing numbers with nonsense symbols as quickly as possible (30). The higher the score on this test, the better a person is able to concentrate.

Social functioning and social support
Social functioning was measured with the social interaction subscale of the SIP. Social support was measured by the Van Sonderen Social Support Inventory (SSL) (31). The SSL was divided into the SSL-I (amount of social support interactions), the SSL-D (discrepancies between amount of social support and desired amount of social support), and the SSL-N (amount of negative interactions). Total scores of SSL-I and SSL-D range from 34-136, total score of SSL-N from 7-28.

Pain
Pain intensity was assessed by a 0 – 100 rating Visual Analogue Scale (VAS) of average pain intensity on current moment, where 0 = no pain and 100 = pain as bad as could be. In addition, pain was measured with the daily-observed pain (DOP) score of the SOL during two weeks. Severity of pain was reported four times a day on a 5-point scale (0-4). Mean scores range from 0 to 16 (17).

Muscle strength
Muscle strength was determined using the Medical Research Council (MRC) grading scale (MRC; 0 to 5) investigating the strength of the shoulder abductors, grip force, foot extensors and knee extensors (32). In order to characterise the patients, these eight values (both left and right) were averaged.

Statistics
Data analysis was performed using SPSS for Windows (version 12.0). Descriptive statistics were used to describe the sample. Normality was tested according to the Kolmogorov-Smirnov test. Group differences at baseline were tested using one-way ANOVAs. In case of an overall significance, the Bonferonni correction was applied to compare the three patient groups. P values < 0.05 were regarded as statistically significant. Non-parametric tests such as the Kruskal-Wallis test and Chi^2 test were used when appropriate.
Paired sample T-tests were performed to analyse differences between baseline and follow-up scores. Pearson correlations were used to analyse relations between the dependent variables (experienced fatigue and impairment at follow-up) and the independent variables (various

dimensions at baseline). Significant variables will be selected as predictors for experienced fatigue and/or functional impairment and were be put in the model of experienced fatigue.
The models were tested with structural equation modelling techniques, and the computer programme AMOS 5.0 was used to test and modify models (33,34). We tested a measurement model with directly observed variables in which the error terms associated with the observed variables were left to be estimated and also were assumed to be uncorrelated with each other. Chi square statistics and the adjusted goodness-of-fit-index (AGFI) were used to test data fit. According to guidelines for structural modelling, the data were considered to fit the model when the Chi square statistics was not significant and the AGFI was high (preferably above 0.90). Furthermore, the population error of approximation (root mean square error of approximation (RMSEA)) was taken into account as a measure of discrepancy per degree of freedom. Values up to 0.05 indicate a close fit and values up to 0.08 represent reasonable errors of approximation in the population. Preferably, the 90% confidence interval (90% CI) of the RMSEA index would be between 0.00 and 0.10 (35,36).

RESULTS

From the 217 participating patients at baseline, 19 patients dropped out for several reasons during the 18-month period of study (e.g. taking part in research takes too much time, family circumstances). In total, 198 patients (60 FSHD, 70 MD and 68 HMSN patients) completed the whole study. The patients who refused to take part in the study did not differ from the participating subjects with regard to age, gender, marital status, level of education, and employment status and level of experienced fatigue in each neuromuscular disorder.

Information on baseline demographic characteristics of the groups are summarized in Table 10.1. No statistically significant differences were found in age, gender, marital status and level of education between the three groups. The mean time between baseline and follow-up was 18 months (sd 2.6) for the whole group.

TABLE 10.1. Baseline demographic characteristics of the three neuromuscular patient groups

	FSHD N=60 mean (sd)	**MD** N=70 mean (sd)	**HMSN-I** N=68 mean (sd)
Mean age	44.3 (9.9)	41.3 (9.6)	42.4 (9.7)
Age range	22-61	22-57	20-59
Gender (male/female)	58% / 42%	57% / 43%	43% / 57%
Higher education (>= 12 years)	16 (27%)	16 (23%)	19 (28%)

Fatigue and functional impairment at baseline and follow-up

For the group of FSHD patients the mean CIS-fatigue score at baseline was 31.8 (11.9), and at follow up 33.7 (12.1) (p=0.11); for the MD patients the CIS-fatigue at baseline was 33.8 (10.3),

and at follow-up 36.5 (9.8) (p=0.006); and for the HMSN patients the CIS-fatigue at baseline was 34.4 (13.0), and at follow-up 33.9 (12.4) (p=0.63).
For the group of FSHD patients the mean functional impairment at baseline was 404.2 (413.5), and at follow up 452.0 (469.5) (p=0.14); for the MD patients the functional impairment at baseline was 605.6 (484.0), and at follow-up 682.5 (489.6) (p=0.008); and for the HMSN patients the functional impairment at baseline was 449.9 (338.3), and at follow-up 434.9 (345.4) (p=0.55).

Correlations between dimensions, fatigue and impairment
In the whole group, correlations between the two dependent variables (CIS-fatigue and impairment at follow-up) and the various dimensions at baseline were calculated (Table 10.2). The following dimensions correlated significantly with experienced fatigue at follow-up: physical activity, sleep disturbances, neuropsychological impairment, pain, and muscle strength. Impairment correlated significantly with the dimensions physical activity, psychological distress, sleep disturbances, neuropsychological impairment, social functioning, pain, and muscle strength. The development of the model was based on the significant correlations between the dimensions and experienced fatigue and/or impairment. The variables of the various dimensions that correlated highest with fatigue and/or impairment were put (one by one) in the initial model.

Development of a model of fatigue
The testing and modification of the model of fatigue was a multi-stage process. Results for each stage are presented in Table 10.3.
Stage 1
The cause and effect relationships for the initial model (Figure 10.1) were defined as follows:
Muscle strength at baseline can be expected to have a direct effect on the level of physical activity (r=-0.540, p=0.00); lower level of physical activity at baseline is related to the level of fatigue at follow-up. We already know that fatigue is associated with functional impairment in daily life (16). In this model, we hypothesized that functional impairment at follow-up was caused by the level of fatigue at follow-up and the level of physical activity (SIP-ambulation) at baseline. The model was rejected as the Chi^2 was significant and the Adjustment Goodness of Fit Index (AGFI) was low.

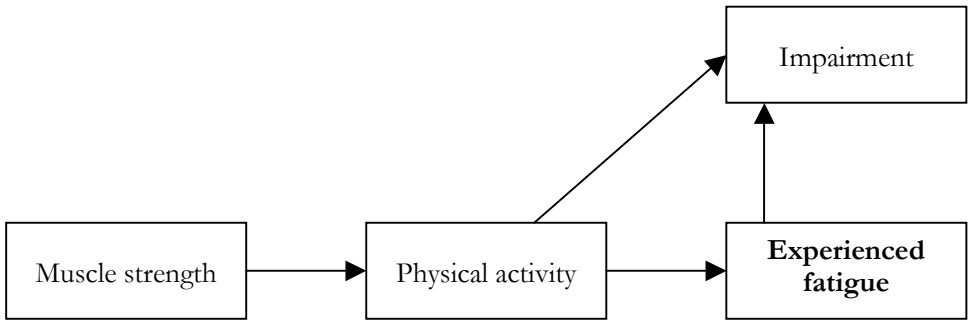

FIGURE 10.1. The hypothesized model (initial model) on dimensions to experienced fatigue in patients with three neuromuscular disorder

TABLE 10.2. Correlation coefficients between the two dependent variables (CIS-fatigue at follow-up and Impairment at follow-up and the various dimensions at baseline in patients with three neuromuscular disorders.

Dimensions Baseline	TOTAL group (N=198)		FSHD (N=60)		MD (N=70)		HMSN (N=68)	
	CIS-fatigue FU	Impairment FU	CIS-fatigue FU	Impairment FU	CIS-fatigue FU	Impairment FU	CIS-fatigue FU	Impairment FU
Physical activity								
SIP-ambulation	0.349**	0.656**	0.447**	0.612**	0.257*	0.660**	0.489**	0.669**
SIP-mobility	0.232**	0.618**	0.301*	0.757**	0.092	0.600**	0.327**	0.473**
actometer	-0.316**	-0.423**	-0.338**	-0.380**	-0.182	-0.376**	-0.422**	-0.518**
Psychological distress								
BDI-pc	0.187	0.202*	0.234*	0.241**	0.209	0.196	0.178	0.198
SCL-anxiety	0.199	0.123	0.208	0.208	-0.027	0.160	0.215	0.289
SCL-depression	0.192	0.234*	0.207	0.187	0.219	0.302*	0.258*	0.246
Sleep disturbances								
SCL-sleep	0.148	0.240*	0.291*	0.534**	-0.010	0.289*	0.281*	0.158
Daily general quality sleep	-0.432**	-0.151*	-0.382**	-0.168	-0.391**	-0.158	-0.539**	-0.359**
Non restorative sleep	0.261**	0.177	0.201	0.225	-0.237*	-0.143	0.492**	-0.167
Neuropsychological impairment								
CIS-concentration	0.202*	0.189	0.212	0.235	0.230	0.205	0.203	0.169
SIP-alertness behaviour	0.198	0.301*	0.201	0.403*	0.223	0.301*	0.165	0.244*
CRT								
RT1	0.105	0.078	0.101	0.110	0.104	0.047	0.105	0.064
RT2	0.156	0.085	0.174	0.179	0.035	0.066	0.177	0.129
RT3	0.132	0.186	0.154	0.263*	0.144	0.112	0.051	0.147
MT1	0.066	0.106	0.172	0.185	0.085	0.117	0.013	0.148
MT2	0.079	0.158	0.183	0.164	0.036	0.146	0.018	0.142
MT3	0.121	0.164	0.185	0.197	0.039	0.114	0.093	0.192
Symbol Digit Test	0.071	0.097	0.069	0.099	0.078	0.123	0.053	0.082
Social functioning/ social support								
SIP-social functioning	0.197	0.442**	0.223	0.645**	0.206	0.412*	0.161	0.309*
SSL-Discrepancies	0.196	0.186	0.194	0.206	0.156	0.152	0.201	0.197
SSL-Interactions	0.125	0.002	0.120	0.084	0.075	0.039	0.127	-0.137
SSL-Negative interactions	0.197	0.182	0.135	0.135	0.206	0.063	0.085	0.095
Pain								
Daily Observed Pain (DOP)	0.279**	0.163*	0.433**	0.450**	0.246*	0.003	0.341**	0.309*
VAS (pain)	0.246**	0.177*	0.499**	0.500**	0.073	0.190	0.155	0.122
Muscle strength								
MRC	-0.265**	-0.193*	-0.335*	-0.208	-0.148	-098	-0.305*	-0.264*

** correlation is significant at the level of 0.01 (2-tailed), and * correlation is significant at the 0.05 level (2-tailed).

Stage 2

The next highest correlation with fatigue at follow-up is sleep disturbances at baseline, especially the daily general sleep quality (Table 10.2). We expected that sleep disturbances (general quality of sleep) would have a direct effect on the level of fatigue. Testing of the new model showed that the AGFI increased to 0.90.

Stage 3

Pain is a common symptom in patients with neuromuscular disorders. Pain (Daily Observed Pain score) at baseline was related to fatigue. We expected that pain would have a direct causal effect on the level of fatigue. Testing this new model showed a good fit as the Adjustment Goodness of Fit Index was well above 0.90 and the Chi^2 statistic was not significant. The Root Mean Square Error of Approximation (RMSEA) was less than 0.05 indicating a close fit for the model.

Stage 4

Social functioning at baseline (SIP-social interaction) was related with impairment at follow-up. We expected that social functioning would have a direct causal effect on impairment. Testing this new model showed that the AGFI decreased to 0.87.

Stage 5

We deleted social functioning from the model. Neuropsychological impairment at baseline (SIP-alertness behaviour) was related to impairment at follow-up. We expected that neuropsychological impairment has a direct causal effect on impairment. Testing this model showed that the AGFI was 0.86.

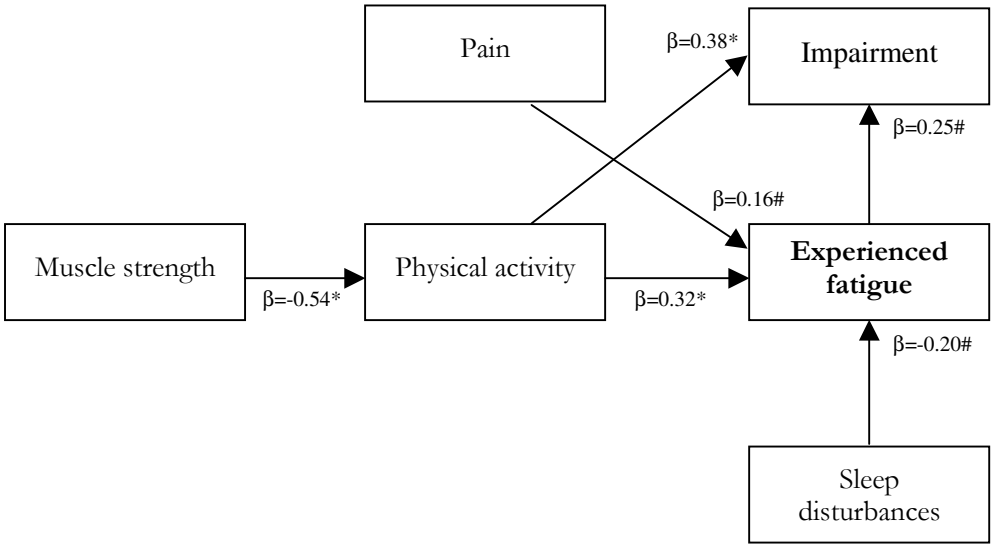

FIGURE 10.2. Adjusted model of perpetuating factors of experienced fatigue in patients with three neuromuscular disorder (n=198), error terms have been omitted in the figure. *p<0.001, #p<0.05.

Stage 6

We deleted neuropsychological impairment from the model. Psychological distress at baseline (SCL-depression) was related with impairment at follow-up. We expected that psychological distress would have a direct causal effect on impairment. Testing of this model showed that the AGFI was reduced to 0.92.

Stage 7

We deleted psychological distress from the model. Muscle strength (MRC score) at baseline was related to impairment at follow-up. We expected that muscle strength would have a direct causal effect on impairment. Testing this model showed that the AGFI reduced to 0.93, compared to stage 3.

Stage 8

The model of stage 3 was chosen as the final model , because it had the best model fit (Figure 10.2).

In stead of a self-report measure for physical activity we used the actometer (actual level of physical activity) as measure for physical activity in the whole group (n=198). The model fit was still acceptable.

TABLE 10.3. Stages in AMOS analyses for neuromuscular disorders (n=198): Chi², degrees of freedom, p-value of Chi² , and Adjusted Goodness of Fit Index (AGFI), and root mean square error of approximation (RMSEA).

Stage	Description of the model (added or deleted causal relations)	Chi²	df	p	AGFI	RMSEA, lower and upper bound
Stage 1	Testing of the initial model: rejected	15.27	2	0.000	0.82	0.13, 0.05 – 0.22
Stage 2	Added: sleep disturbances to fatigue	13.9	4	0.007	0.90	0.11, 0.05 - 0.11
Stage 3	Added: pain to fatigue	4.75	6	0.576	0.97	0.00, 0.00 – 0.10
Stage 4	Added: social functioning to impairment	28.77	8	0.000	0.87	0.12, 0.07 – 0.16
Stage 5	Deleted: social functioning					
	Added: neuropsychological impairment to impairment	33.1	8	0.000	0.86	0.13, 0.08 – 0.17
Stage 6	Deleted: neuropsychological impairment					
	Added: psychological distress to impairment	16.35	8	0.038	0.92	0.07, 0.02 – 0.12
Stage 7	Deleted: psychological distress					
	Added: muscle strength to impairment	9.8	5	0.082	0.93	0.07, 0.00 – 0.14
Stage 8	Deleted: muscle strength to impairment					
	Final Model (stage 3)	4.75	6	0.576	0.97	0.00, 0.00 – 0.10
	Alternative model:					
	Actometer instead of a self-report measure for physical activity	14.2	6	0.027	0.92	0.08, 0.02 – 0.14

Model fit of final model and alternative model in the various neuromuscular disorders

The relationships between the various dimensions to fatigue and impairment in daily life might vary substantially with the neuromuscular disorder. For that reason the model fit of the final model (stage 8) was tested for the three neuromuscular disorders separately.

For HMSN patients the model fit was excellent (AGFI 0.98). In the FSHD patients the model fit of the final model was lower (AGFI 0.94). In FSHD we found a relationship between pain and physical activity (r= 0.499), which was not found in MD and HMSN patients. Therefore, in the FSHD group we added a relationship between pain and physical activity in the final model, the model fit increased (AGFI 0.97) (Table 10.4). In MD patients the model fit was the lowest (AGFI 0.95).
In the three neuromuscular disorders separately we also tested the alternative model with the actometer in stead of the self report measure of physical activity (Table 10.4). In HMSN patients (AGFI 0.96) and FSHD patients (AGFI 0.94) the model fit was still excellent. However, in MD patients the model fit reduced considerably (AGFI 0.84).

TABLE 10.4. The final model for the various neuromuscular disorders: Chi^2, degrees of freedom, p-value of Chi^2 , and Adjusted Goodness of Fit Index (AGFI),and root mean square error of approximation (RMSEA)

Disorder	**Description of the model** (added or deleted causal relations)	**Chi^2**	**df**	**p**	**AGFI**	**RMSEA, lower and upper bound**
MD	Testing the final model	2.82	6	0.831	0.95	0.000, 0.00 – 0.09
	Testing the alternative model	10.1	6	0.122	0.84	0.100, 0.00 – 0.20
HMSN	Testing the final model	1.99	6	0.926	0.98	0.000, 0.00 – 0.05
	Testing the alternative model	3.20	6	0.784	0.96	0.000, 0.00 – 0.11
FSHD						
Stage 1	Testing the final model	3.73	6	0.714	0.94	0.000, 0.00 – 0.11
	Testing the alternative model	5.0	6	0.543	0.91	0.000, 0.00 – 0.15
Stage 2	Added: pain to physical activity	5.21	5	0.390	0.97	0.000, 0.00 – 0.10
	Testing alternative model	6.84	5	0.341	0.94	0.030, 0.00 – 0.12

DISCUSSION

As far as we know this is the first longitudinal study in which a model has been developed and tested with factors involved in the perpetuating of experienced fatigue in patients with neuromuscular disorders.
The investigated neuromuscular disorders are slowly progressive disorders. These patients had perhaps more time to adapt their lifestyle on various dimensions to the daily hassles of their disease. In a time lag of 18 months we found that the MD patients reported significant higher levels of experienced fatigue and increased functional impairments. In FSHD and HMSN patients we found no differences in the level of experienced fatigue and functional impairments.
Model testing revealed that muscle strength, level of self-reported physical activity, sleep disturbances, and pain were significantly associated with the level of experienced fatigue. Level of experienced fatigue and level of physical activity were significantly associated with more functional impairment in daily life. This model showed an excellent fit for the whole group of patients.

For the separate neuromuscular disorders, the model fit is excellent for the HMSN, also when actual level of physical activity was used. In FSHD patients the relation between pain and activity has to be added in order to get an acceptable fit. In MD the model fit reduced considerably after replacing self-reported physical activity by actual physical activity.

Physical activity has an important place in the model of fatigue in neuromuscular disorders. The same is found in other conditions, e.g., CFS and fatigue after cancer (18,19). Lower level of actual physical activity contributed to higher levels of experienced fatigue and more functional impairment in daily life in several diseases.

Physical activity was measured by self-report in the final model. Self-report instruments do not measure actual behaviour. Responses on these instruments appear to be an expression of the patients' view about activity, and may be biased by cognitions concerning illness and disability (37). Self-report instruments of physical activity reflect subjective interpretation of the level of physical activity, and not the actual level of physical activity (38). Therefore, an actometer was used as a reference for actual level of physical activity. Accelerometers, such as the actometer used in the present study, are reliable and valid instruments to measure human physical activity (38). In general, correlations between the actometer and self-reported measures of physical activity are moderate (38,19).

Our investigations showed that actual physical activity levels by actometer differed considerably between the three neuromuscular disorders. In patients with myotonic dystrophy we found no difference in actometer scores between severely fatigued patients and non-severely fatigued patients, but in FSHD and HMSN patients we found significant differences between severely fatigued and non-severely fatigued patients on actometer score. This means that in FSHD and HMSN was a relationship between actual level of physical activity and experienced fatigue, but not in MD. When we tested the model with the actometer instead of the self-report measure in FSHD and HMSN patients the model fit remains excellent. But in MD patients the model fit reduced considerably. The discrepancy between self-report and actual behaviour appear to be larger in MD compared to FSHD and HMSN. These findings also suggest that factors other than physical fitness play a role in MD.

Psychological distress, social functioning and neuropsychological impairment at baseline could not be included in the final model. These factors do no add by the factors already presented in the model.

Some pharmaceutical agents may influence the measurements by changing (neuro)functioning. While about a third of our neuromuscular patients used any form of medication, we checked if this could explain the higher values of fatigue in our group pf patients. Subgroup analyses, however, showed that fatigue values of only medication-free patients were also increased.

The strengths of this study are the longitudinal character of it and the fact that it concerns a large group of patients. A limitation is that the subgroups of patients are rather small. Therefore the presence of more differences between the three patient groups could not be tested. The number of factors to be tested in the model is limited with a small number of patients. Another point is the generality of the results. We only investigated ambulant patients and excluded total wheelchair bounded patients, to measure the actual level of physical activity in these disorders. So the model is probably not valid for more severe patients. However, fatigue scores from 381 non-

participating patients with neuromuscular disorders (74 FSHD, 243 MD, and 64 HMSN patient) did not differ from the participating patients (1).

The model of perpetuating factors of experienced fatigue in three neuromuscular disorders might serve as a basis for treatment approaches to reduce fatigue in these disorders. The model of perpetuating factors of fatigue in FSHD and HMSN is different from the model of MD. The main difference is seen in physical (in)activity. These differenced have implications for interventions based on these models. Programmes with comprehensive aerobic exercise would be maximise the level of actual physical activity and reduce fatigue in patients with FSHD and HMSN. Successful treatment of fatigue in FSHD and HMSN should not be directed only at encouraging patients to increase physical activity level but, in addition, sleep disturbances and pain should also be treated.

REFERENCES

1. Engel AG, Franzini-Armstrong C. Myology, 3rd edition. New York: McGraw-Hill, 2004.
2. Dyck PJ, Thomas PK. Peripheral neuropathy, 4th edition. London: Saunders, 2005.
3. Padberg GW, Lunt PW, Koch MC, Fardeau M. Diagnostic criteria for facioscapulohumeral muscular dystrophy. Neuromusc Disord 1991; 1(4): 231-234.
4. Harper PS. Myotonic dystrophy, 3rd version. London: Harcourt Publishers Ltd, 2001.
5. Gabreels-Festen AA, Bolhuis PA, Hoogendijk JE, Valentijn LJ, Eshuis EJ, Gabreels FJ. Charcot-Marie-Tooth disease type 1A: morphological phenotype of the 17p duplication versus PMP22 point mutations. Acta Neuropathol (Berl) 1995; 90(6): 645-649.
6. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004; 363: 978-988.
7. Krupp LB, Fatigue. Philadelphia: Butterworth Heinemann, 2003.
8. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord 2001; 16: 190-196.
9. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology 1993; 43: 2016-2018.
10. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. Mov Disord 1999; 14: 237-241.
11. Werf van der S, van der Broek H, Anten H, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur J Neurol 2001; 45 (1): 28-33.
12. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
13. Sunnerhagen KS, Grimby G. Muscular effects in late polio. Acta Physiol Scand 2001; 1771: 335-340.
14. Paul RH, Cohen RA Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
15. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune-mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
16. Kalkman JS, Schillings ML, van der Werf SP, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.
17. Vercoulen JH, Swanink CM, Galama JM, Fennis JF, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.

18. Vercoulen JH, Hommes OR, Swanink CM, Galama JM, Fennis JF, van der Meer JW, Bleijenberg G. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
19. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients : a cross-sectional study. Ann of Oncol 2002 ; 13: 589-598.
20. Vries M de, Soetekouw PM, Meer van der JW, Bleijenberg G. Fatigue in Cambodia veterans. QJM 2000; 93: 283-289.
21. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 157-170.
22. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. The sickness impact profile; results of an evaluation study of the Dutch version. Ned Tijdschr Geneeskd 1990; 134(40): 1950-1954.
23. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19(8): 787-805.
24. van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000; 49(5): 373-379.
25. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
26. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behav Res Ther 1997; 35: 785-791.
27. Arindell WA, Ettema JHM. SCL-90, handleiding bij een multidimensionele psychopathologie-indicator. Amsterdam: Swets & Zeilinger BV, 1986.
28. Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, van der Wilt G, Spinhoven P, van der Meer JWM. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-847.
29. Houx PJ, Jolles J. Age-related decline of psychomotor speed: effects of age, brain health, sex, and education. Percept Mot Skills 1993; 76: 195-211.
30. Stinissen J, Willems PJ, Coetsier L, Hulsman WLL. Handleiding bij de Nederlandse bewerking van de WAIS. (Manual of the Dutch edition of the WAIS). Amsterdam: Swets and Zeitlinger, 1970.
31. Van Sonderen E. Sociale Steun Lijst-Interacties (SSL-I) en Sociale Steun Lijst-Discrepanties (SSL-D). Groningen: Noorderlijk Centrum voor Gezondheidsvraagstukken, 1993.
32. Medical Research Council. Aids to the examination of the peripheral nerve injuries. London: her Majesty's Stationery Office, 1981:1.
33. Arbuckle JL, Wothke W. Amos 4.0 user's guide. Chicago, IL: Smallwater Corporation, 1999.
34. Arbuckle JL. Amos 5.0 updat to the Amos user's guide. Chicago, IL: Smallwater Corporation, 2003.
35. Bollen KA. Overall fit in covariance structure models. Two types of sample size effects. Psychol Bull 1990; 107: 256-259.
36. Browne MW, Cudeck R. Alternative ways of assessing model fit. In Bollen KA, Long JS eds. Testing structural equation models. Newburt Park: Sage Publications, 1993.
37. Leventhal H, Diefenbach MLEA. Illness cognition: Using common sense to understand treatment adherence and affect cognition interaction. Cogn Ther Res 1992; 16: 143-163.
38. Vercoulen JH, Bazelmans E, Swanink CM, Fennis JF, Galama JM, Jongen PH, Hommes O, van der Meer JW, Bleijenberg G. Physical activity in chronic fatigue syndrome: Assessment and its role in fatigue. J Psychiat Res 1997; 31: 661-673

CHAPTER 11

General discussion

INTRODUCTION

The aim of this thesis is to investigate fatigue from prevalence to predictors, and to develop a model of perpetuating factors of fatigue in three homogeneous groups of patients with different genetically well-defined neuromuscular disorders, using a longitudinal study design. These three neuromuscular disorders are the following: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; adult-onset myotonic dystrophy (MD), a multisystem disorder; and hereditary motor and sensory neuropathy type I (HMSN), a neurogenic disorder.
In this final chapter we will discuss the main results of this thesis and place them into perspective, as well as describe the limitations of our investigations. In Part 1 we will discuss the prevalence of experienced fatigue in patients with the three neuromuscular disorders (FSHD, MD, and HMSN), factors related to experienced fatigue, the lack of a connection between psychiatric comorbidity and fatigue, the relationship between ambulatory disabilities, walking aids, and fatigue, and finally, the various types of fatigue (experienced fatigue and physiological fatigue). Our model of perpetuating factors of fatigue in neuromuscular disorders will be discussed in Part 2 and suggestions for clinical implications and future research will be made in Part 3.

PART 1

1.1 Prevalence of experienced fatigue in patients with neuromuscular disorders

Fatigue in multiple sclerosis (MS) is much better known and more frequently studied (1-4) than it is in neuromuscular disorders. More than 60% of patients with MS report severe experienced fatigue and assessments with validated questionnaires in various samples of MS patients have consistently confirmed that experienced fatigue is a frequent problem and a problem with a serious impact on daily life. Experienced fatigue is considered to be an established clinical symptom of MS (1-4).
Within the group of neuromuscular disorders, fatigue has been described in patients with post-polio syndrome, myasthenia gravis, and immune-mediated neuropathies like Guillain-Barré syndrome (5-9). These studies demonstrate that fatigue is a prominent and highly disabling symptom in the neuromuscular disorders investigated. All these studies had a cross-sectional design and not one of them investigated the relationship between fatigue and impairment in daily life, or the relationship between fatigue and physical activity. To our knowledge, fatigue has never been studied in relatively frequent neuromuscular disorders like FSHD, MD or HMSN.
Our first goal, therefore, was to assess the prevalence of experienced fatigue in these patient groups by means of a validated fatigue questionnaire, the Checklist Individual Strength (10-11). The Checklist Individual Strength has excellent psychometric properties and it has been used in research and in clinical practice in patients with several disorders and in healthy controls (11-13). A cut-off score was determined on this scale to assess severe experienced fatigue (11).
The results of the studies reported in this thesis show that experienced fatigue is a severe problem for more than 60% of patients with FSHD, adult-onset MD, and HMSN type I. These data confirm the clinical impression that the majority of patients with these types of

neuromuscular disorders suffer from severe fatigue, demonstrating that the experience of severe fatigue is not only characteristic of multiple sclerosis, but is a frequent complaint in the said disorders as well.
In the case of all three neuromuscular disorders studied, severely fatigued patients reported more limitations in daily life than non-severely fatigued patients, in the areas of physical functioning for instance, pain, social functioning, mental health, work, and leisure time.
The conclusion is warranted that fatigue is not only a frequent complaint, but also a relevant, clinically important problem with tremendous implications for the quality of life of these patients.

1.2. Factors related to experienced fatigue
In addition to the prevalence of experienced fatigue, we also studied the factors that are related to fatigue in the three different neuromuscular disorders. As indicated in Chapter 1, we used a multi-dimensional assessment method that was developed, tested and validated in cross-sectional and prospective studies of several chronic disorders (1,11-13).
We may conclude from the results of our studies that severely fatigued patients with different neuromuscular disorders scored significantly higher on all dimensions compared with non-severely fatigued patients with the same disorder.
In addition, we found several differences between severely fatigued and non-severely fatigued patients in the three investigated neuromuscular disorders. In patients with MD, the severely fatigued patients had higher scores on communication problems, sleep disturbances and concentration problems, and more difficulties with initiating and planning than the non-severely fatigued patients, and these scores were also higher than in FSHD and HMSN. Patients with FSHD or HMSN with severe fatigue appeared to have lower levels of actual physical activity. Remarkably, in MD we found no difference in actual physical activity between severely fatigued and non-severely fatigued patients.
Regression analyses were used to study the relationships between the different dimensions and fatigue. Although the factors contributing to fatigue differed somewhat among the disorders, the most important finding was that the amount of explained variance of fatigue differed considerably in the three neuromuscular disorders, with the amount of explained variance being the highest for HMSN and the lowest for MD. These data are cross-sectional, however, which makes it difficult to draw definite conclusions about the cause and effect relationships between variables.
The longitudinal study of these factors might reveal which factors have predictive value for chronic fatigue (Part 2).

1.3. Psychiatric comorbidity is not an explanation for severe fatigue in these disorders
Experienced fatigue is a symptom in a number of affective disorders, including depression and dysthymia. Depression turned out to be a predictor of low health-related quality of life in several chronic neurological diseases (14-16) and the studies in question show that symptoms of depression have an appreciable effect on quality of life. Depressive symptoms have been linked to more functional impairment and increased levels of fatigue (17-20), which led us to study the relationship between experienced fatigue and psychiatric disorders (including depressive disorders) in FSHD, MD, and HMSN patients.

We found that approximately 11% of the patients with these neuromuscular disorders probably had a current psychiatric disorder, while more than 60% of the patients reported severe experienced fatigue. The presence of current psychiatric disorders in the neuromuscular disorders investigated did not differ from the presence of psychiatric disorders in the Dutch population (the 1-month prevalence of mood and anxiety disorders is 14%) (21). The most common psychiatric disorders in our groups were depression and phobias. No differences were found between the three neuromuscular disorders with regard to the presence of psychiatric comorbidity. In contrast to studies of patients with Parkinson's disease (range of psychiatric disorders 15-30%) and multiple sclerosis (range 20-35%) (15,19,20), we found a much lower rate of psychiatric disorders in our sample of patients with neuromuscular disorders, even in the subgroup of adult-onset MD.
More importantly, psychiatric comorbidity was not associated with the severity of experienced fatigue. The prevalence of experienced fatigue appeared to be as high in patients without psychiatric comorbidity as in the group with psychiatric comorbidity, and the same was true for patients with and without depression. This means that experienced fatigue cannot be considered to be part of a depression in these patients. In contrast to other neurological disorders (MS, Parkinson's disease), psychiatric comorbidity is not an explanation for experienced fatigue in FSHD, MD, and HMSN.

1.4. Ambulatory disability, walking aids, and fatigue

Most hereditary neuromuscular disorders have a clinical course characterized by progressive muscular weakness and atrophy that – over a period of years - involves general mobility problems, the most serious of which are loss of independent walking ability and dependence in daily living activities. Patients with HMSN may also develop foot deformities due to muscular imbalance (22). Functional disability of ambulation in HMSN patients has been reported previously in the literature (22-28) and while ambulation and mobility-related problems were investigated in these studies, none of them investigated the relationship between ambulatory disability, walking aids, and experienced fatigue.
HMSN patients are usually not wheelchair-bound and so many young and middle-aged patients who walk independently are regarded as non-disabled or mildly- disabled in the literature (24-26). In our study, however, we found that ambulation disabilities occur frequently in ambulant patients with HMSN type I and that this presence of ambulatory disabilities appeared to be associated with experienced fatigue. In addition, the use of walking aids was related to fewer ambulatory problems and less fatigue. Half of the patients who reported ambulatory disabilities did not use any form of walking aid and had higher fatigue scores, which could mean that the use of walking aids is helpful in reducing fatigue, a finding that is of interest in the rehabilitation management of the patient.

1.5. Different types of fatigue (experienced fatigue and physiological fatigue)

It is particularly interesting to study the contribution of physiological factors to experienced fatigue in patients with neuromuscular disorders in whom the motor of the body itself (the muscles and/or peripheral nervous system) is affected.

Physiological fatigue is defined as the loss of force-producing capacity during exercise. This loss is called peripheral fatigue if has its origin at the peripheral nerve or in the muscle tissue (29-31), and it is called central fatigue if it occurs because of changes in the central nervous system during exercise (31-33). Central activation failure is present when voluntary central activation is sub-optimal and the increase of central activation failure during exercise is called central fatigue (figure 11.1).

Experienced fatigue is the complaint of the patient that can be heard in the physician's consulting room and it can only be assessed by self-report. Physiological fatigue (peripheral fatigue and central fatigue) cannot be reported, but only assessed in a laboratory setting and experienced fatigue does not necessarily correlate with signs of physiological fatigue (30).

A main finding for physiological fatigue is that central activation is diminished or decreases faster in patients who experience severe fatigue (Chapter 6); sub-optimal activation means that the motor unit firing rate or motor unit recruitment is sub-optimal. Figure 11.1 illustrates the concepts of fatigue and central activation failure in controls and patients with three different neuromuscular disorders during sustained maximal voluntary contraction (MVC). Central activation failure is about 15% at the start of contraction in healthy controls (left panel), which means that the maximal voluntary contraction is about 15% lower than maximal muscle capacity. The amount of central activation failure increases during sustained maximal voluntary contraction, implying that central fatigue occurs.

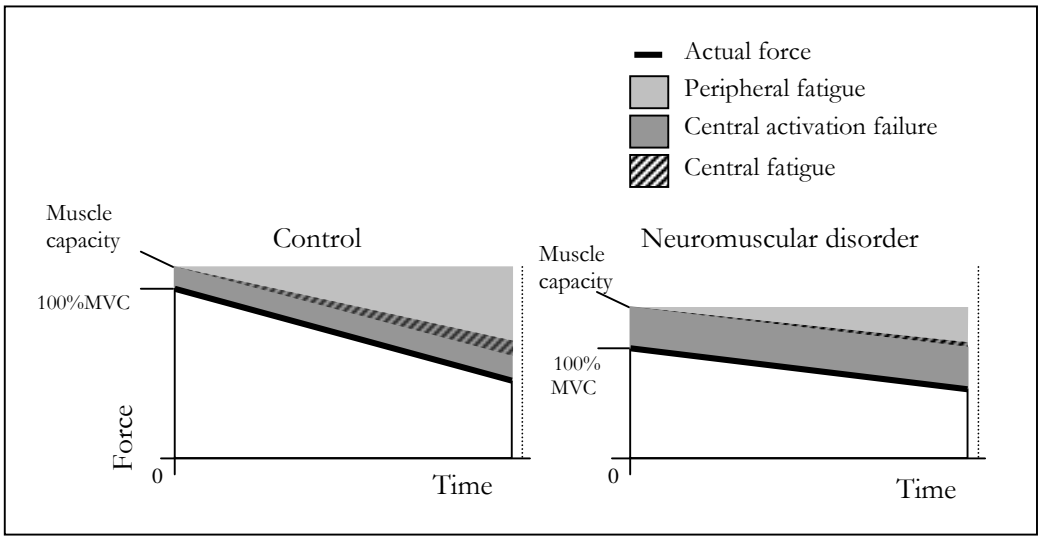

FIGURE 11.1. Peripheral fatigue, central fatigue and central activation failure in healthy controls and in patients with one of three different neuromuscular disorders (FSHD, MD, and HMSN). Vertical bars on the right of every figure show a constant force level in the panels.

In contrast, the maximum muscle capacity is reduced in patients with FSHD, MD or HMSN (right panel), as a direct consequence of peripheral changes due to the disease. Moreover, high values for central activation failure further decrease force production during maximal voluntary contraction. Hardly any central fatigue occurred in the neuromuscular disorders studied.

The amount of peripheral fatigue or rate of peripheral fatigue development is lower in the three neuromuscular disorders than in healthy controls. To a large extent, this is probably caused by the fact that patients perform the task at a lower absolute force level.
The studies presented in this thesis (Chapter 6 and Chapter 7) indicate that central activation failure and central fatigue are related to experienced fatigue. Central activation failure explained 6 to 10% of the variance in the level of experienced fatigue in the three different neuromuscular disorders, which means that central activation has a weak relationship with experienced fatigue. We also found no relationship between peripheral fatigue and experienced fatigue and we therefore consider physiological fatigue (peripheral fatigue and central activation failure) and experienced fatigue to be largely separate types of fatigue.

PART 2

2.1. The building of a model of experienced fatigue

The availability of a model of perpetuating factors of fatigue in three different neuromuscular disorders may help to develop treatment approaches to reduce fatigue in these disorders, and we therefore developed and tested a model of factors involved in the persistence of experienced fatigue in these three neuromuscular disorders, using the "structural equation modelling" statistical technique. This technique does not only make it possible to test different relationships simultaneously, but also to compare the data fit of two or more proposed models. The longitudinal study enabled us to investigate predictors of the natural course of experienced fatigue and we examined the relationship possible perpetuating factors at baseline and fatigue at follow-up. The data of the three patient groups had to be combined in order to have enough power to test the models, the disadvantage of this procedure being that we focus on the common factors instead of the differences.

We found that physical activity, sleep disturbances, pain and muscle strength are predictors of experienced fatigue in the combined group of FSHD, MD, and HMSN patients. This means that patients who reported lower levels of physical activity, more sleep disturbances, more pain, and patients with increased muscle weakness, are the ones that are most likely to experience persistent fatigue. In the final model (Chapter 10), physical activity is the most important predictor of fatigue, followed by sleep disturbances and pain.
The following elements for the building of a model of perpetuating factors of fatigue in neuromuscular disorders will be discussed in part 2: sleep disturbances and fatigue, pain and fatigue, influence of close relatives on fatigue, illness cognitions and fatigue, and finally, differences between the three separate neuromuscular disorders.

2.2. Sleep disturbances and fatigue

Sleep disturbances are common in patients with chronic neurological disorders (34-38), problems with sleep maintenance (light and fragmented sleep) and difficulties with sleep initiation being the most frequent sleep disorders in neurological disorders. Other common sleep-associated complaints include excessive daytime sleepiness and nocturnal pain and cramps (37).

Although fatigue is a common finding in a wide range of sleep disorders and has been documented in clinical reports, it has not been studied as an independent symptom in the context of sleep disturbances (39-41). No studies were found that investigated the relationship between sleep disturbances and fatigue in patients with FSHD, MD or HMSN.
We measured sleep disturbances with validated questionnaires and a standardised sleep complaint diary, in which patients reported the perceived sleep disturbances on a daily basis (e.g. quality of sleep, unrestorative sleep, hours of sleep, wake-up time and bedtime).
Sleep disturbances showed an important relationship with experienced fatigue in all three disorders and perceived quality of sleep was admitted in the final model of fatigue for the whole group. There are some differences in sleep disturbances, however, between the three neuromuscular disorders. We found that patients with MD reported more time to sleep and rest during the day than patients with FSHD or HMSN, and we also found that one third of the participating MD patients reported excessive daytime sleepiness, although the length of sleep during the night was similar in FSHD, MD, and HMSN patients.
HMSN patients reported significantly more sleep problems than the patients in the two other groups (Chapter 7). The former reported more problems with falling asleep and maintaining sleep and we found a significantly higher standard deviation in the bedtimes of HMSN patients than in the two other groups, which means that the bedtimes for HMSN patients vary to a greater extent than the bedtimes of the other patient groups. Furthermore, patients with FSHD showed greater variability in wake-up time than MD and HMSN patients.
Previous studies found an association between sleep disturbances, depression and fatigue (42-43), but we found a very low rate of depression in the patients investigated and no relationship with fatigue, which means that the low prevalence of depression cannot explain the high rate of sleep disturbances in these disorders. Even if we see depression as a continuum, using the Beck depression inventory, the correlation between depression and different kinds of sleep parameters is low. In conclusion, sleep disturbances had a direct relationship with fatigue, which was not affected by depression.

2.3. Pain and fatigue

Pain is a symptom that most clinicians would not typically associate with chronic neuromuscular disorders. Clinical experience in our hospital had indicated, however, that many patients with FSHD, MD or HMSN report pain and consider it an important problem. Few studies have examined pain and the effect of pain on the daily lives of patients with slowly progressive neuromuscular disorders (44-47) and these showed considerable variability in the frequency of pain in the different disorders. Severe pain appears to be more common among patients with muscular dystrophies and post-polio syndrome and less common in patients with other neuromuscular disorders (47). Most of these studies investigated pain in heterogeneous groups of neuromuscular disorders and had a cross-sectional design; none of them investigated the relationship between pain and physical activity, and pain and fatigue in neuromuscular disorders.
Our first goal was to assess the prevalence of pain in patients with FSHD, MD or HMSN, by means of validated pain questionnaires and a standardised pain complaint diary.
We found that about three-quarters of the FSHD and HMSN patients and nearly half of the MD patients report pain (Chapter 8). In all three neuromuscular disorders, the pain scores were higher

than the scores of a reference group of healthy people, which means that pain is a clinically relevant complaint in these patients. The localization of pain was specific for each neuromuscular disorder, with pain being most frequently localized in body regions mostly affected by the neuromuscular disorder, so that localization differed among the three disorders. In the three groups, we found no differences in functional impairment and in muscle strength between patients with and without pain, signifying that pain is not related to impairment and muscle strength in the whole group of patients. Only in FSHD patients did we find a relationship between pain and physical activity, whereby FSHD patients with higher pain levels showed lower levels of physical activity. In contrast to the findings relating to pain, however, higher levels of fatigue in all patient groups were consistently associated with higher levels of functional impairment and lower levels of physical activity. Pain and experienced fatigue were related in FSHD and HMSN patients, but unrelated in MD patients. Pain is an important feature in the neuromuscular disorders investigated, therefore, although fatigue has more implications for daily functioning.

2.4. Influence of close relatives on fatigue

The emphasis in research has been primarily on the person with the disease and the disease process itself, rather than on the system that includes the close relatives. It is well known that patients with chronic disorders may often disorganize the lives of close relatives and change the family's lifestyle, with recent evidence supporting the concept that close relatives influence the mental and physical status of patients with chronic disorders, e.g. in patients with Parkinson's disease (48-53).

The partner relationship is generally thought to be one of the most important sources of social support, because the partner is the main provider of emotional and instrumental support for the patient. Rhommessen et al investigated spouse responses to behaviours that patients exhibit as a result of their disability (e.g. activity limitations, difficult ambulation, or discomfort) (49) and their study shows that some spouses may unwittingly encourage decreased patient functioning by being overly solicitous or attentive to patient disability behaviour. Research on individuals with chronic pain demonstrates that negative spouse responses to disability are associated with greater discomfort and emotional distress in the patient (54), so that the reaction of the spouse to the patient's disability may affect physical and psychological adjustment in the patient. This finding for the spouse may also apply to close relatives of the patient, especially in cases where a spouse is lacking.

Although spouses and close relatives are important resources for the patient with a chronic disorder (53), the role of spouses or close relatives of patients with neuromuscular disorders has received no attention as yet.

As a consequence, we investigated the responses of close relatives to experienced fatigue of patients with FSHD, MD or HMSN (Chapter 9) and found that sympathetic-empathic responses by the relative to the fatigue of the patient, such as getting help or attention and advising the patient to rest, contributed to higher levels of experienced fatigue in the patients; many close relatives advised the severely fatigued patient to rest, for example. This means that such sympathetic-empathic responses by the close relatives may reinforce behaviour that increases the chances of higher levels of fatigue in the patient. It has also been suggested that social processes

in the family system of patients increased their dependency on others and decreased the self-efficacy of the patient (54).
We did not include the responses of close relatives in our model of fatigue in neuromuscular disorders, because the responses of the relatives were collected exclusively in the follow-up study and we only wanted to include factors assessed at baseline in our model of fatigue. Furthermore, the sample size in a model assessing responses of close relatives would have been much smaller than in our final model, due to the fact that not every patient had a close relative who was willing to fill in the relatives' questionnaires.

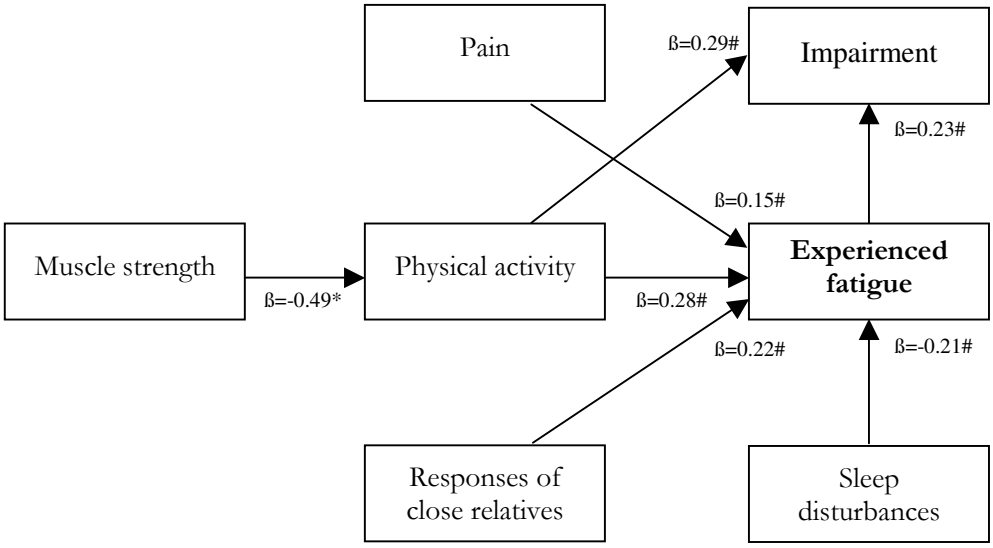

FIGURE 11.2. The model of perpetuating factors of fatigue including the sympathetic-empathic responses of close relatives. (N=106: FSHD, n=33; MD, n=32; HMSN, n=41). *p<0.001, #p<0.05.

The model fit is 0.88 if we only include patients from the close relatives study (n=106) in our final model. If the sympathetic-empathic responses of the close relatives are added to the model as a direct influence on the experienced fatigue of the patient, the model fit increases to 0.92 (Figure 11.2), which means that the responses of close relatives are one of the perpetuating factors of fatigue in the neuromuscular disorders. The implications of these findings indicate the importance of including close relatives in treatment and of teaching close relatives to reinforce healthy behaviour.

2.5. Illness cognitions and fatigue

Illness cognitions are seen as a risk factor for an unfavourable physical and psychological health status in patients with various chronic diseases (55), but have never been studied in neuromuscular disorders before. Illness cognitions reflect the way patients perceive and think about their disease and are considered important mediators between disease and the well-being of the patient. These illness cognitions relate to different aspects of the disease, such as beliefs about the cause of the disease, the consequences of the disease, and the sense of control over

symptoms (self-efficacy). In addition, illness cognitions can also affect disease-related behaviour, such as the perception of symptoms, coping with complaints, seeking help and compliance with treatment (56). According to Bandura's social learning theory, people's behaviour is strongly influenced by self-efficacy expectations (57) and it has been demonstrated that illness cognitions also play an important role in the models of persistence of fatigue in chronic fatigue syndrome and multiple sclerosis (58). In these models, self-efficacy was directly and independently related to fatigue severity.

We also found for all three disorders that the severely fatigued patients reported a lower sense of control over fatigue than the non-severely fatigued patients (Chapter 7). Our model of perpetuating factors of fatigue in neuromuscular disorders did not include illness cognitions in the final model, however, for the following reason. Those patients who reported that they did not experience fatigue as a symptom did not fill out the self-efficacy and causal attribution questionnaires, thereby considerably reducing the number of patients in whom we could test the model. The model fit is excellent (AGFI 0.94) if we test our model in severely fatigued patients alone (n=109) and there is only a small increase in model fit (AGFI 0.95) if the model includes self-efficacy at baseline associated with experienced fatigue at follow-up. Lower self-efficacy expectations are moderately associated, therefore, with higher levels of experienced fatigue in neuromuscular disorders.

2.6. Differences between the three neuromuscular disorders

In this thesis we have found that the majority of patients with FSHD, MD or HMSN experienced severe fatigue and the longitudinal study enabled us to investigate predictors of experienced fatigue. We combined the data of the three patient groups in order to have enough power to test the models, but we wanted to know the specific perpetuating factors for fatigue in each neuromuscular disorder (FSHD, MD, and HMSN), which is why the model comprising the factors of the final model was tested for the three neuromuscular disorders separately. The model fit remained excellent for HMSN, but was lower in FSHD, in which we found a significant relationship between pain and physical activity that was not found in HMSN and MD, and which led us to add a relationship between pain and physical activity in the FSHD model in order to get a better fit. The model fit remained the lowest in MD and could not be improved.

The model of fatigue used self-reported physical activity in all three neuromuscular disorders and it is known that there can be a considerable discrepancy between *self-reported* physical activity and *actual level* of physical activity (actometer). At the same time, the highest levels of self-reported physical activity were seen in HMSN and FSHD and the lowest in MD. The model fit remained excellent when we tested the model with the actometer instead of the self-report measure in FSHD and HMSN (Figure 11.3A and 11.3B), but the already lower model fit in MD decreased considerably after replacing self-reported physical activity by actual level of physical activity (Figure 11.3C). The actual level of physical activity is the most important predictor of fatigue in the models of fatigue for FSHD and HMSN, followed by sleep disturbances, which means that the actual level of physical activity was a perpetuating factor in FSHD and HMSN, but not in MD.

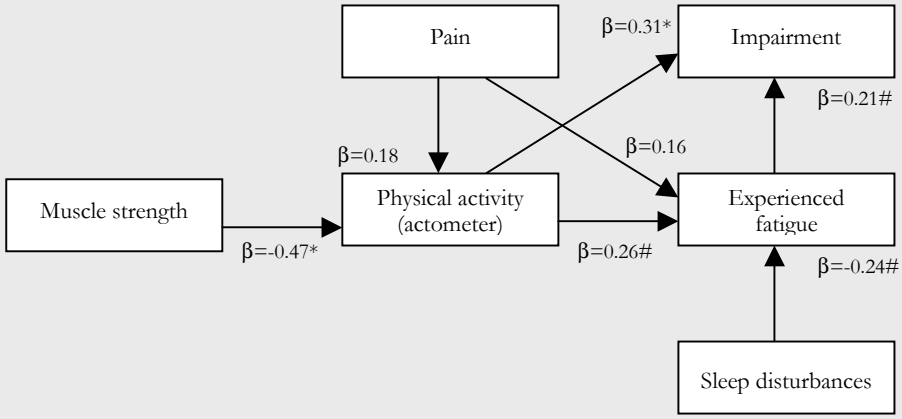

FIGURE 11.3A. The model of perpetuating factors of fatigue in the FSHD group (N=60). AGFI=0.94, *p<0.001, #p<0.05.

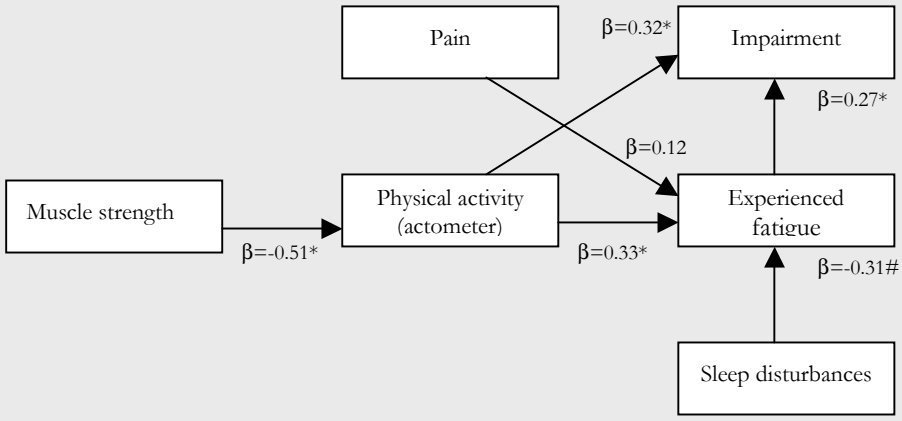

FIGURE 11.3B. The model of perpetuating factors of fatigue in the HMSN group (N=68). AGFI=0.96, *p<0.001, #p<0.05.

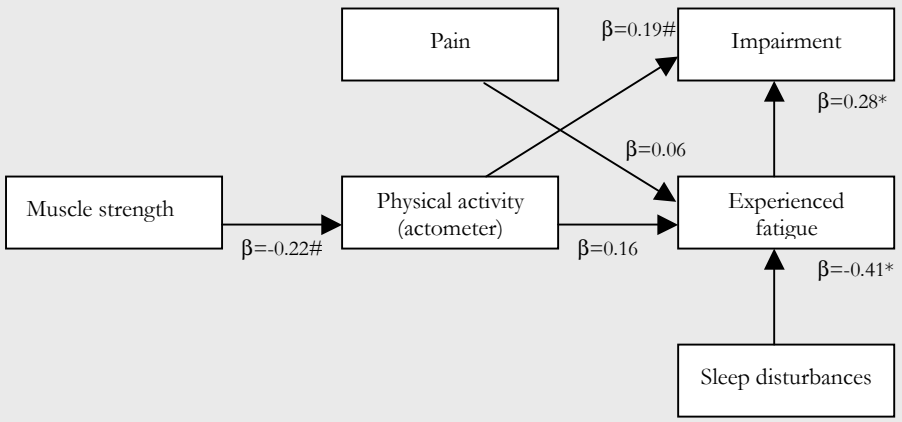

FIGURE 11.3C. The model of perpetuating factors of fatigue in the MD group (N=70). AGFI=0.84, *p<0.001, #p<0.05.

FIGURE 11.3. The different models of perpetuating factors for the various neuromuscular disorders.

These findings suggest that factors other than the actual level of physical activity play a role in patients with MD. In Chapter 3, we found that patients with MD have higher levels of reduced motivation than FSHD and HMSN patients; reduced motivation, which means the drive to initiate and sustain interest in a specific activity, is a well-known problem in MD (58-59). Excessive daytime sleepiness is another established clinical manifestation of MD (59) and measured with the Epworth Sleepiness Scale, we found that one third of the participating MD patients reported excessive daytime sleepiness. Although it could be argued that MD patients may confuse the experience of fatigue with daytime sleepiness, previous research (60) and our data as well showed that excessive daytime sleepiness was related to reduced motivation, but not to the level of experienced fatigue, which is why we could not admit excessive daytime sleepiness into the model of fatigue in MD.
Recent evidence has shown a role for the CNS stimulant Modafinil as a therapeutic agent to help control excessive daytime sleepiness in patients with MD (61-65), but we expect Modafinil to have no effect on fatigue severity in these patients, because fatigue exists independently of excessive daytime sleepiness in MD.
The model of perpetuating factors of fatigue in FSHD and HMSN is different from the model in MD, the main difference being seen in physical (in)activity. These differences have implications for interventions based on these models.

PART 3

3.1. Generalizability of the model of fatigue

We developed a model of fatigue in patients with FSHD, MD, and HMSN, but the question is whether this model of fatigue is suitable for treatment approaches to fatigue in all these patient groups and there are arguments why this is not the case. The model is based on data from ambulant patients. We only investigated ambulant patients and excluded totally wheelchair-bound patients in order to be able to use an actometer to measure actual level of physical activity in these neuromuscular disorders. No differences in fatigue severity were found between eligible and non-eligible patients in the three combined groups of neuromuscular disorders. In the FSHD group, however, we found a significant difference in self-reported ambulatory impairments between eligible and non-eligible patients, but not in the MD group or HMSN group. It is possible, therefore, that the model of fatigue would be different in more severely affected FSHD patients in particular, e.g. patients with more ambulatory impairments.

3.2. Clinical implications and future research

Our findings show that fatigue is a *common* symptom in patients with FSHD, MD, and HMSN. Additionally, we have demonstrated that experienced fatigue is a *relevant* problem, because it is related to more severe impairments in these disorders. We conclude from this that fatigue is an important issue to be addressed in the neuromuscular clinic and we would like to draw clinical conclusions in this paragraph from the data of this thesis.

Firstly, it is important that clinicians actively ask the patient and the close relatives about the presence and consequences of fatigue and to distinguish it from depression, sleep disturbances and exercise intolerance. The Abbreviated Fatigue Questionnaire (AFQ) could be used in addition to the medical history to assess fatigue severity (66); this questionnaire was developed for use in clinical practice and has good reliability and validity. A cut-off score on this questionnaire was determined to assess severe experienced fatigue.
Next, the clinician can check the known perpetuating factors of fatigue in the individual patient (e.g., physical inactivity, sleep disturbances and pain) and can also consider simple treatment approaches, such as prescribing walking aids in order to reduce physical inactivity, since physical inactivity is the main factor among the perpetuating factors of fatigue in these neuromuscular disorders. Furthermore, it may be worthwhile to involve close relatives in the conversation with the patient about fatigue and to stimulate close relatives to reinforce healthy behaviour in the patient.

The model of perpetuating factors of fatigue in the three neuromuscular disorders can serve as a basis for future studies of treatment approaches to reduce fatigue in these disorders. The model shows that different factors affect fatigue, directly or indirectly, which means that treatment approaches will have to be multi-factorial. The level of actual physical activity is the most important factor to treat in FSHD and HMSN, but not in MD. Other factors are sleep disturbances, pain, influence of close relatives, and illness cognitions. All of these factors may be contained in treatment approaches to reduce fatigue.

What is already known about influencing physical activity and the effect on fatigue in patients with FSHD, MD, and HMSN?
The literature demonstrates that strength training and aerobic exercise training are well tolerated and safe interventions with limited positive effect on muscle strength (67-71). All of these studies have substantial (methodological) shortcomings, however, their main shortcoming being the absence of fatigue measurements. Furthermore, most published studies grouped the different neuromuscular disorders together, while we know that FSHD, HMSN and MD have different perpetuating factors of fatigue, which is the reason why conclusions on the effect of training derived from mixed populations cannot be readily extrapolated to patients with specific neuromuscular disorders. The usefulness of aerobic exercise training to improve the level of actual physical activity will be relevant for FSHD and HMSN, but not for MD patients, because of differences in predictors of fatigue based on our model of perpetuating factors.
Interventions to reduce fatigue can be developed and tested for FSHD and HMSN based on the model derived from this thesis. Other studies are needed for MD, however, before interventions for fatigue can be developed for this patient group.

REFERENCES

1. Vercoulen JH, Hommes OR, Swanink CM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996; 53: 642-649.
2. Pittock SJ, Mayr WT, McClelland RL et al. Quality of life is favourable for most patients with multiple sclerosis: a population-based cohort study. Arch Neurol 2004; 61: 679-686.
3. Benedict RHB, Wahlig E, Baksic R et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behaviour change. J Neurol Sci 2005; 231: 29-34.
4. Mitchell AJ, Benito-León J, Morales Gonzáles J-M, Rivera-Navarro J. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. Lancet Neurol 2005; 4: 556-566.
5. Paul RH, Cohen RA Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenis gravis. Muscle Nerve 2000; 23: 1402-1406.
6. Berlly MH, Strauser WW, Hall KM. Fatigue in Postpolio Syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.
7. Stibrant Sunnerhagen K, Grimby G. Muscular effects in late polio. Acta Physiol Scand 2001; 1771: 335-340.
8. Merkies ISJ, Schmitz PIM, Samijn JPA, van der Meche FGA, van Doorn PA. Fatigue in immune-mediated polyneuropathies. Neurology 1999; 53: 1648-1654.
9. Hughes RAC, Wijdicks EFM, Benson E, Cornblath DR et al. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol 2005; 62: 1194-1198.
10. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. J Psychosom Res 2004; 56: 157-170.
11. Vercoulen JH, Swanink CM, Fennis JF et al. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-392.
12. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients : a cross-sectional study. Ann of Oncol 2002; 13: 589-598.
13. Vries M de, Soetekouw PM, Meer van der JW, Bleijenberg G. Fatigue in Cambodia veterans. QJM 2000; 93: 283-289.
14. Carson AJ, Postma K, Stone J, Warlow C, Sharpe M .The outcome of depressive disorders in neurology patients: a prospective cohort study. J Neurol Neurosurg Psychiatry 1993; 74: 893-896.
15. Schrag A. Psychiatric aspects of Parkinson's disease, an update. J Neurol 2004; 51:795-804.
16. Surtees PG, Wainwright NWJ, Khaw KT, Day NE. Functional health status, chronic medical conditions and disorders of mood. Br J Psychiatry 2003; 183: 299-303.
17. Holroyd S, Currie LJ, Wooten GF. Depression is associated with impairment of ADL, not motor function in Parkinson disease. Neurology 2005; 64: 2134-2135.
18. Lou JS, Reeves A, Benice T, Sexton G. Fatigue and depression are associated with poor quality of life in ALS. Neurology 2003; 60: 122-123.
19. Lobentanz IS, Asenbaum S, Vass K et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand 2004; 110: 6-13.
20. Jamardhan V, Bakshic R. Quality of life in patients with multiples sclerosis: the impact of fatigue and depression. J Neurol Sci 2002; 205: 51-58.
21. Bijl RV, Ravelli A, van Zessen G.Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998; 33:587-595.
22. Birouk N, Gouider R, Le Guern E, et al. Charcot-Marie-Tooth disease type 1A with 17p11.2 duplication. Clinical and electrophysiological phenotype study and factors influencing disease severity in 119 cases. Brain 1997; 120.5: 813-823.

23. Jannink MJ, Ijzerman MJ, Groothuis-Oudshoorn K, Stewart RE, de Groot JW, Lankhorst GJ. Use of orthopedic shoes in patients with degenerative disorders of the foot. Arch Phys Med Rehabil 2005; 86 : 687-692.
24. Pfeiffer G, Wicklein EM, Ratusinski T, Schmitt L, Kunze K. Disability and quality of life in Charcot-Marie-Tooth disease type I. J Neurol Neurosurg Psychiatry 2001; 70: 548-550.
25. Piccininni M, Falsini C, Pizzi A. Quality of life in hereditary neuromuscular diseases. Acta Neurol Scand 2004; 109: 113-119.
26. Vinci P, Serrao M, Millul A, de Santis F et al. Quality of life in patients with Charcot-Marie-Tooth disease. Neurology 2005; 65: 922-924.
27. Verhamme C, van Schaik IN, Koelman JH, de Haan RJ, Vermeulen M, de Visser M. Clinical disease severity and axonal dysfunction in hereditary motor and sensory neuropathy Ia. J Neurol 2004; 251: 1491-1497.
28. Vinci P, Perelli SL. Footdrop, foot rotation, and plantarflexor failure in Charcot-Marie Tooth disease. Arch Phys Med Rehabil 2002; 83.4: 513-516.
29. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001; 81: 1725-1789.
30. Kent-Braun JA. Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. Eur J Appl Physiol Occup Physiol 1999; 80: 57-63.
31. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004; 363: 978-988.
32. Shield A, Zhou S. Assessing voluntary muscle activation with the twitch interpolation technique. Sports Med 2004; 34: 253-267.
33. Allman BL, Rice CL. Neuromuscular fatigue and aging: central and peripheral factors. Muscle Nerve 2002; 25: 785-796.
34. Hossain JL, Ahmad P, Reinish LW, Kayumo L, Hossain NK, Shaprio CM. Subjective fatigue and subjective sleepiness: two dependent consequences of sleep disorders? J Sleep Res 2005; 14: 245-253.
35. Happe S, Berger K. The influence of poor sleep on quality of life in patients with Parkinson's disease. A prospective study. Somnology 2003; 7: 134-139.
36. Happe S, Klosch G. Lorenzo J, Kunz D, et al. Perception of sleep: Subjective versus objective sleep parameters in patients with Parkinson's disease in comparison with healthy elderly controls. J Neurol 2005; 252: 936-943.
37. Shapiro CM, Devins GM, Hussain MRG. Sleep problems in patients with medical illness. Br Med J 1993; 306: 1532-1535.
38. Turek FW, Dugovic C, Zee PC. Current understanding of the circadian clock and the clinical implications for neurological disorders. Arch Neurol 2001; 58: 1781-1787.
39. Ohayon MM, Shapiro CM. Sleep and fatigue. Semin Clin Neuropsychiatry 2000; 5: 56-57.
40. Lichstein KL, Means MK, Noe SL, Aguillard RN. Fatigue and sleep disorders. Behav Res Ther 1997; 35: 733-740.
41. Buchwald D, Pascualy R, BombardierC, Kith P. Sleep disorders in patients with chronic fatigue syndrome. Clin Infect Dis 1994; 18: 68-72.
42. Shapiro CM. Sleep disruption as a cause and consequence of psychiatric illness. Can J Diagn 2000; 11: 2-5.
43. Baran AS, Richter AC. Obstructive sleep apnoea and depression. CNS Spectr 2003; 8: 120-134.
44. Bushby KMD, Pollitt C, Johnson MA, Rogers MT, Chinnery PF. Muscle pain as a prominent feature of facioscapulohumeral muscular dystrophy (FSHD): four illustrative case reports. Neuromusc Disord 1998; 8: 574-579.
45. Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtee LD, Beardsley RM, Abresch RT, Bird TD. Neuropathic pain in Charcot-Marie-Tooth Disease. Arch Phys Med Rehabil 1998; 79: 1560-1564.

46. Abresch RT, Carter GT, Jensen MP, Kilmer DD. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. Am J Hosp Palliat Care 2002; 19: 39-48.
47. Jensen MP, Abresch RT, Carter GT, McDonald CM. Chronic pain in persons with neuromuscular disease. Arch Phys Med Rehabil 2005; 86: 1155-1163.
48. Chió A, Gathier A, Calvo A, Ghilione P, Matani R. Caregiver burden and patients' perception of being a burden in ALS. Neurology 2005; 64: 1780-1782.
49. Rhommessen B, Aarsland D, Braekhus A, Oksengaard AR, Engedal K, Laake K. The psychological burden on spouses of the elderly with stroke, dementia and Parkinson's disease. Int J Geratr Psychiatry 2002; 17: 78-84.
50. Whetten-Goldstein K, Sloan F, Kulas E, Cutson T, Schenkman M. The burden of Parkinson's disease on society, family, and the individual. J Am Geriatr Soc 1997; 45: 844-849.
51. Bisschop MA, Kriegsman DMW, Beekma ATF, Deeg DJH. Chronic disease and depression: the modifying role of psychosocial resources. Soc Sci Med 2004; 59: 721-733.
52. Sneeuw KCA, Sprangers MAG, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life in patients with chronic disease. J Clin Epidemiol 2002; 55: 1130-1143.
53. Glozman JM. Quality of life in caregivers. Neuropsych Review 2004; 14: 183-196.
54. Turk DC. Understanding pain suffers: the role of cognitive processes. Spine J 2004; 4: 1-7.
55. Jerant AF, von Friedreichs-Fitzwater MH, Moore M. Patients' perceived barriers to active self-management of chronic conditions. Patient Edu Couns 2005; 57: 300-307.
56. Leventhal H, Diefenbach MLEA. Illness cognition: using common sense to understand treatment adherence and affect cognition interaction. Cogn Ther Res 1992; 16: 1431-1463.
57. Bandura A. Social foundations of thought and action: a social cognitive theory. Englewood Cliffs, NJ: Prentice Hall: 1986.
58. Vercoulen JH, Swanink CM, Galama JM et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: Development of a model. J Psychosom Res 1998; 45: 507-517.
59. Machuca-Tzili L, Brook D, Hilton-Jones D. Clinical and molecular aspects of the myotonic dystrophies: A review. Muscle Nerve 2005; 32: 1-18.
60. Harper PS, van Engelen BGM, Eymard B, Wilcox DE. Myotonic dystrophy: present management, future therapy. New York: Oxford University Press, 2004.
61. Werf van der S, Kalkman J, Bleijenberg G, van Engelen B, Schillings M, Zwarts M. The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult onset myotonic dystrophy. J Neurol Neurosurg Psychiatry 2003; 74: 138-139.
62. Van Engelen BGM, Eymard B, Wilcox D. 123rd ENMC International workshop: management and therapy in myotonic dystrophy, 6-8 February 2004, Naarden, The Netherlands. Neuromuscul Disord 2005; 15: 389-394.
63. Damian MS, Gerlach A, Schmidt F, Lehmann E, Reichmann H. Modafinil for excessive daytime sleepiness in myotonic dystrophy. Neurology 2001; 56: 794-796
64. Talbot K, Strading J, Crosby J, Hilton-Jones D. Reduction in excessive daytime sleepiness by modafinil in patients with myotonic dystrophy. Neuromuscul Disord 2003; 13: 1876- 1880.
65. MacDonald JR, Hill JD, Tarnopolsky MA. Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy. Neurology 2002; 59: 1876-80.
66. Alberts M, Vercoulen JH, Bleijenberg G. Assessment of fatigue. The practical utility of the subjective feeling of fatigue in research and clinical practice. In: Vingerhoets A, editor. Assessment in behavioral medicine. Brunner Routledge; 2001. p. 301-27.
67. van der Kooi EL, Vogels OJM, van Asseldonk RJGP, Lindeman E, Hendriks JCM, Wohlgemuth M, van der Maarel SM, Padberg GW. Strength training and albuterol in facioscapulohumeral muscular dystrophy. Neurology 2004; 63: 702-708.

68. Lindeman E, Leffers P, Spaans F, Drukker J, Reulen J, Kerckhoffs M, Köke A. Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: a randomized clinical trial. Arch Phys Med Rehabil 1995; 76: 612-620.
69. van der Kooi EL. Lindeman E, Riphagen I. Strength training and aerobic exercise training for muscle disease (Review). The Cochrane Library 2005, Issue 1.
70. Ørngreen MC, Olsen DB, Vissing J. Aerobic training in patients with myotonic dystrophy type 1. Ann Neurol 2005; 57: 754-757.
71. Olsen DB, Ørngreen MC, Vissing J. Aerobic training improves exercise performance in facioscapulohumeral muscular dystrophy. Neurology 2005: 64; 1064-1066.

SUMMARY

Fatigue is a common symptom in a number of (chronic) neurological disorders such as multiple sclerosis, Parkinson's disease, and stroke. Surprisingly, fatigue in neuromuscular disorders received little attention.
This thesis is the result of cooperation between the Expert Centre Chronic Fatigue and the Neuromuscular Centre Nijmegen of the Radboud University Medical Centre in Nijmegen.
In this thesis we studied patients with three homogeneous groups of genetically well-defined neuromuscular disorders: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; adult-onset myotonic dystrophy (MD), a multisystem disorder; and hereditary motor and sensory neuropathy type I (HMSN), a neurogenic disorder.
Fatigue is a multidimensional symptom and therefore it is important to find factors that perpetuate fatigue. A conceptual model of fatigue as it relates to neuromuscular disorders is needed to serve as a framework for research and discourse. The longitudinal design enabled us to investigate predictors of fatigue in these disorders. In Chapter 1 a general introduction to the studies is give.
Literature reviewed in Chapter 2 has already shown the presence of chronic severe fatigue in several diseases. Though, until recently fatigue was seldom recognized as an important symptom of neuromuscular disorders.
In Chapter 3 a study on the prevalence of experienced fatigue in neuromuscular disorders is presented. Severe experienced fatigue is experienced by more than 60% in patients with FSHD, MD, and HMSN type I. In addition, being severely fatigued was associated with greater levels of functional impairment in daily life. Because severe experienced fatigue is associated with problems in physical functioning, social functioning, mental health, bodily pain, and general health perception, it is a clinically and socially relevant problem.
An association between experienced fatigue and psychiatric disorders has been reported in a number of neurological disorders, but has received little attention in neuromuscular disorders so far. Chapter 4 shows that psychiatric comorbidity occurs equally in patients with adult-onset MD, FSHD, HMSN-I, which is comparable to that in the Dutch general population. The most common psychiatric disorders were depression and phobias. This chapter shows that current and lifetime psychiatric comorbidity is not associated with experienced fatigue and/or muscle strength in these disorders.
Chapter 5 shows that ambulatory related disabilities frequently occur within a large homogeneous population of HMSN I patients. Walking aids were used by 49% of the patients. Furthermore, ambulatory disabilities are related with age, muscle strength, experienced fatigue, actual level of physical activity (actometer), and general perceived health status. Walking aids are generally administrated to the more severely affected patients, however, the use of walking aids appears to be not completely in accordance with the perceived disability.
Especially in patients with neuromuscular disorders, affecting the muscles and/or nerves, it is interesting to study the contribution of physiological factors to experienced fatigue. Physiological

fatigue is defined as the loss of force producing capacity during exercise. Both peripheral and central factors contributed to physiological fatigue, indicating that both the muscle tissues and the central nervous system may be involved. Chapter 6 describes that in the overall group of patients with neuromuscular disorders central activation is reduced. However, the inter-individual distribution of the levels of central activation is much larger and a clear overlap exists between patients and healthy controls. A significant correlation exists between the value of central activation failure at the start of the sustained maximal voluntary contraction and the level of experienced fatigue. Again, the amount of peripheral fatigue is reduced, probably because of the lower maximal voluntary contraction of patients.

Chapter 7 shows that experienced fatigue is related to central activation failure, but not to peripheral fatigue in a large cohort of patients with FSHD, adult-onset MD, and HMSN type I. However, central activation failure explained only a small amount of the variance of experienced fatigue. Experienced fatigue, central activation failure, and peripheral fatigue appeared to be separate types of fatigue with different determinants. There was no significant difference in central activation failure, peripheral fatigue or muscle strength between severely experienced fatigued and non-severely experienced fatigued patients. The respective determinants of experienced fatigue appear to be quite similar in the three neuromuscular disorders, but the amount of explained variance differs.

Chapter 8 shows that three-quart of the FSHD and HMSN patients, and nearly half of the MD patients reported regularly pain. Pain complaints were most frequently localized in body regions affected in the course of the neuromuscular disorder and thus differ between the three disorders. The most common type of pain was muscle pain. There was no relationship between the presence of pain and age, gender, functional disability, actual level of physical activity (actometer), and muscle strength in all three disorders. We found a weak relation between pain and experienced fatigue. We can conclude that pain and experienced fatigue are different features in these neuromuscular disorders.

Experienced fatigue have a major impact on patients' functioning and activities of daily living. The effects are not limited to the patient, the close relatives of the patient can suffer as well.

Chapter 9 shows that responses of close relatives to both experienced fatigue and neuromuscular disorder of the patient were mainly sympathetic-empathic responses and similar within relatives of patients with the three disorders. The relatives reported that they were trying to imagine what the patients feels, making supportive statements. Overall, the relatives rated the level of experienced fatigue of the patient lower than the patient did himself. We found low agreement between relatives and MD patients over the patients' experienced fatigue and higher agreement between relatives and FSHD and HMSN patients.

In spouse living together we found more disagreement in marital satisfaction within MD couples than within FSHD and HMSN couples. Sympathetic-empathic responses of close relatives to fatigue of the patient were related to higher levels of experienced fatigue in FSHD and HMSN patients, but not in MD patients.

Chapter 10 is a sequel of our cross-sectional study of fatigue in neuromuscular disorders of which the results were presented in the first chapters. The longitudinal design of this study enabled us to investigate the perpetuating factors of fatigue.

In all three neuromuscular disorders, muscle strength, self-reported activity, sleep disturbances and pain at baseline contributed directly or indirectly, to fatigue and impairment at follow-up. Lower muscle strength contributed to lower levels of physical activity, which in turn contributed to experienced fatigue severity. The model showed excellent fit for the whole group of neuromuscular disorders. In FSHD, also pain contributed to physical activity. A model with the actometer as measurement for actual physical activity in stead of self-report showed an excellent model fit in FSHD and HMSN, but an insufficient fit in MD. In conclusion, the model of perpetuating factors for fatigue in FSHD and HMSN is different from the model in MD. The main difference is in physical (in)activity. These differences have implications for interventions based on these models.

The general discussion in chapter 11 mainly concerns the building of a model of experienced fatigue in neuromuscular disorders. A model of fatigue is the basis to develop treatment interventions to reduce fatigue in these disorders. The differences between the three neuromuscular disorders are important for treatment interventions. Future studies will have to develop treatment interventions and to determine other factors that may reduce fatigue in these disorders.

SAMENVATTING

Vermoeidheid is een veel voorkomend symptoom in een groot aantal (chronische) neurologische aandoeningen zoals multiple sclerose, ziekte van Parkinson en cerebrovasculaire aandoeningen. Het is opmerkelijk dat vermoeidheid in neuromusculaire aandoeningen nauwelijks aandacht heeft gekregen.
Dit proefschrift betreft een samenwerking tussen het Nijmeegs Kenniscentrum Chronische Vermoeidheid en het Neuromusculaire Centrum Nijmegen van het Universitair Medisch Centrum St. Radboud in Nijmegen.
In dit proefschrift worden patiënten uit drie homogene genetisch neuromusculaire aandoeningen onderzocht, te weten facioscapulohumerale dystrofie (FSHD), een spieraandoening; myotone dystrofie (MD), een multisysteem aandoening, en hereditaire motore en sensore neuropathie type I (HMSN), een zenuwaandoening.
Vermoeidheid is een multidimensioneel symptoom en daarom is het belangrijk om instandhoudende factoren van vermoeidheid in neuromusculaire aandoeningen te vinden. Een conceptueel model van vermoeidheid in neuromusculaire aandoeningen is nodig om te komen tot een raamwerk dat gebruikt kan worden voor onderzoek en beloopstudies. De longitudinale studieopzet maakt het mogelijk om predictoren van vermoeidheid in deze aandoeningen te bestuderen. Hoofdstuk 1 behelst een algemene introductie op de verschillende studies.
Hoofdstuk 2 geeft een samenvatting van de literatuur die ernstige ervaren vermoeidheid bij uiteenlopende aandoeningen bespreekt. Bij neuromusculaire aandoeningen wordt vermoeidheid zelden als symptoom herkent.
In Hoofdstuk 3 wordt de prevalentie van ervaren vermoeidheid in neuromusculaire aandoeningen beschreven. Extreme ervaren vermoeidheid komt voor bij meer dan 60% van de patiënten met FSHD, MD en HMSN. De vermoeidheid gaat gepaard met functionele beperkingen, zoals meer problemen op het gebied van fysiek functioneren, sociaal functioneren, mentaal welzijn, pijn en perceptie van gezondheid, in het dagelijks leven en is daarom een klinisch en sociaal relevant probleem.
In verschillende chronische neurologische aandoeningen wordt gevonden dat psychiatrische stoornissen en ervaren vermoeidheid samen hangen. In hoofdstuk 4 wordt gevonden dat psychiatrische stoornissen niet verschillen tussen de drie neuromusculaire aandoeningen en de prevalentie vergelijkbaar is met de prevalentie in de algemene Nederlandse bevolking. De psychiatrische stoornissen die het meest voorkomen zijn depressie en fobische angsten. Dit hoofdstuk laat zien dat huidige en levensloop psychiatrische comorbiditeit niet samenhangen met ervaren vermoeidheid en/of spierzwakte in de onderzochte neuromusculaire aandoeningen.
Hoofdstuk 5 laat zien dat beperkingen op het gebied van lopen frequent voorkomen bij een grote groep patiënten met HMSN type I. Loophulpmiddelen worden door 49% van de patiënten gebruikt. Beperkingen op het gebied van lopen zijn gerelateerd aan leeftijd, spierkracht, ervaren vermoeidheid, feitelijk beweeggedrag, en aan ervaren gezondheidsbeleving. Loophulpmiddelen

worden in het algemeen meer voorgeschreven bij patiënten die meer zijn aangedaan. Echter, het gebruik van deze hulpmiddelen is niet geheel in overeenstemming met de ervaren beperkingen.
Met name in patiënten met neuromusculaire aandoeningen, waarbij de spieren en/of de zenuwen zijn aangedaan, is het interessant om de bijdrage van fysiologische aspecten van ervaren vermoeidheid te bestuderen. Fysiologische vermoeidheid is gedefinieerd als een vermindering van de maximale vrijwillige kracht als gevolg van inspanning. Zowel perifere (spier-) als centrale (zenuwstelsel-) aspecten kunnen aan fysiologische vermoeidheid bijdragen.
Hoofdstuk 6 beschrijft dat bij patiënten met verschillende neuromusculaire aandoeningen de centrale aansturing van de spieren sterk is verminderd. Dit verschil bestaat zelfs op individueel niveau: de centrale activatie is bij iedere onderzochte patiënt kleiner dan bij elke persoon uit de controle groep. Tijdens de meting treedt bij de patiënten minder perifere vermoeidheid op dan bij de controle personen. Dit komt waarschijnlijk doordat de spiercapaciteit door de verslechterde aansturing tijdens de meting in mindere mate aangesproken wordt.
Hoofdstuk 7 toont dat ervaren vermoeidheid gerelateerd is aan het gebrek aan centrale aansturing, maar niet aan perifere vermoeidheid. Echter, het gebrek aan centrale aansturing verklaart slechts een klein gedeelte van de ervaren vermoeidheid. Hieruit concluderen we dat ervaren vermoeidheid, gebrek aan centrale aansturing en perifere vermoeidheid drie verschillende vormen van vermoeidheid zijn. Er werden geen verschillen gevonden tussen ernstig vermoeide patiënten en niet vermoeide patiënten in gebrek aan centrale aansturing, perifere vermoeidheid of in spierkracht. De verschillende determinanten van ervaren vermoeidheid komen overeen tussen de drie verschillende neuromusculaire aandoeningen, maar de verklaarde variantie verschilt sterk tussen de drie aandoeningen.
Driekwart van de patiënten met FSHD en HMSN en bijna de helft van patiënten met MD rapporteren frequent pijn (hoofdstuk 8). Pijnklachten worden met name in die lichaamsdelen aangegeven die gedurende het beloop van de betreffende neuromusculaire aandoening aangedaan raken. Dit zorgt ervoor dat de pijnlokaties verschillend zijn tussen de drie onderzochte aandoeningen. De meest gerapporteerde pijn is spierpijn. Er werd geen relatie gevonden tussen pijn en leeftijd, tussen pijn en sexe, tussen pijn en functionele beperkingen in het dagelijks leven, tussen pijn en actuele fysieke activiteit, en tussen pijn en spierzwakte in alle drie de aandoeningen. Er werd een zwakke relatie gevonden tussen pijn en ervaren vermoeidheid. We concluderen dat pijn en vermoeidheid verschillende factoren zijn in deze neuromusculaire aandoeningen.
Hoofdstuk 9 beschrijft dat partners of andere naaste familieleden met name meevoelend reageren op de vermoeidheidsklachten en de neuromusculaire aandoening van de patiënt. Er is sprake van een lage overeenstemming over de vermoeidheid van de patiënt door de partner en de patiënt zelf in koppels van MD patiënten. Er werd overeenstemming gevonden in koppels van FSHD en HMSN patiënten over de vermoeidheid van de patiënt. Levenspartners van patiënten met MD rapporteren lage huwelijkssatisfactie in tegenstelling tot levenspartners van FSHD en HMSN patiënten. Meevoelende responsen van partners van FSHD en HMSN patiënten hebben invloed op de ernst van de ervaren vermoeidheid van de patiënt, maar dit wordt niet gevonden in MD koppels.
Hoofdstuk 10 beschrijft het vervolg op de cross-sectionele studie naar vermoeidheid bij patiënten met neuromusculaire aandoeningen, waarvan de resultaten in de vorenstaande hoofdstukken worden beschreven. De longitudinale studie van dit onderzoek maakt het mogelijk om

instandhoudende factoren van vermoeidheid te onderzoeken. In alle drie de neuromusculaire aandoeningen vinden we dat spierzwakte, zelf gerapporteerde fysieke activiteit, slaapproblemen en pijn op baseline direct of indirect bijdragen aan ervaren vermoeidheid en beperkingen op follow-up. Toename van spierzwakte draagt bij aan verminderde fysieke activiteit, wat leidt tot toename van de ervaren vermoeidheid. In patiënten met FSHD levert ook pijn een bijdrage aan fysieke activiteit. Een model met de actometer als meetinstrument voor de feitelijke fysieke activiteit in plaats van zelf gerapporteerde fysieke activiteit, toont een goede fit voor patiënten met FSHD en HMSN, maar niet in patiënten met MD. In patiënten met MD vinden we geen samenhang tussen feitelijke fysieke activiteit op baseline en ervaren vermoeidheid bij follow-up in tegenstelling tot patiënten met FSHD en HMSN. Deze bevindingen zijn erg belangrijk voor de ontwikkeling van interventies om vermoeidheid te verminderen in patiënten met een neuromusculaire aandoening.

De algemene discussie in hoofdstuk 11 gaat vooral over de ontwikkeling van het model voor vermoeidheid in patiënten met een neuromusculaire aandoening. Een model voor vermoeidheid is de basis voor de ontwikkeling van behandelingsmogelijkheden om vermoeidheid in deze aandoeningen te verminderen. De verschillen tussen de drie neuromusculaire aandoeningen zijn daarbij zeer belangrijk om een passende behandeling te ontwikkelen. Toekomstig onderzoek zal moeten uitwijzen of behandelingsmogelijkheden vermoeidheid kunnen reduceren in deze aandoeningen.

LIST OF PUBLICATIONS

van Engelen BGM, Kalkman JS, Schillings ML, van der Werf SP, Bleijenberg G, Zwarts MJ. Moeheid bij neuromusculaire aandoeningen (Fatigue in neuromuscular disorders). Ned Tijdschr Geneeskd, 2004; 148 (27): 1336-1341.

Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BGM, Bleijenberg G. Experienced fatigue in Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I. J Neurol Neurosurg Psychiatry 2005; 76: 1406-1409.

Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Psychiatric disorders appear equally in patients with Myotonic Dystrophy, Facioscapulohumeral Dystrophy, and HMSN-I. Acta Neurol Scand, in press.

Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Influence of relatives on fatigue experienced byn Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I. European Neurology, 2006: 56: 24-30.

Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Determinants of experienced and physiological fatigue in Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I. Submitted.

Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. Pain and the relation with fatigue in Facioscapulohumeral Dystrophy, Myotonic Dystrophy and HMSN-I. Submitted.

Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM, Bleijenberg G. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. Submitted.

van der Kooi EL, Kalkman JS, Lindeman E, Hendriks JCM, van Engelen BGM, Bleijenberg G, Padberg GW. Effects of Training and Albuterol on Pain and Fatigue in Facioscapulohumeral Muscular Dystrophy. J Neurology, in press.

de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JWM, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. NeuroImage, 2005; 26: 777-781.

de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JWM, Toni I. Neural Correlates of the Chronic Fatigue Syndrome- an fMRI study. Brain, 2004; 127:1948-1957.

de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JWM, Toni I. Cognitive behavioural therapy increases grey matter in prefrontal cortex. Submitted.

van der Linden MH, Kalkman JS, Hendricks HT, Schillings ML, Zwarts MJ, Bleijenberg G, van Engelen BGM. Ambulatory disabilities, and the use of walking aids in HMSN-I patients. Disability and Rehabilitation, in press.

Schillings ML, Kalkman JS, van der Werf SP, van Engelen BGM, Bleijenberg G, Zwarts MJ. Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. Clin Neurophysiol, 2004 Nov; 115 (11): 2518-2524.

Schillings ML, Kalkman JS, van Engelen BGM, Bleijenberg G, Zwarts MJ. Central fatigue assessed by the readiness potential. Eur J Appl Physiol, in press.

Schillings ML, Kalkman JS, Janssen HMHA, van Engelen BGM, Bleijenberg G, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders. Submitted.

Werf van der S, Kalkman J, Bleijenberg G, van Engelen B, Schillings M, Zwarts M. The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult-onset myotonic dystrophy. J Neurol Neurosurg Psychiatry, 2003; 74: 138-139.

Abstracts in international journals

Kalkman JS, van der Werf SP, van Engelen BGM *et al.* Fatigue complaints are equally characteristic for neuromuscular diseases as for multiple sclerosis. Neuromus Disorders, 2002. p. 779.

Schillings ML, Kalkman JS, Janssen HMHA, van Engelen BGM, Bleijenberg G, Zwarts MJ. Reduced central activation during sustained contraction in neuromuscular disorders. Clin Neurophysiol, 2004.

Schillings ML, Kalkman JS, Janssen HMHA, van Engelen BGM, Bleijenberg G, Zwarts MJ. Diminished central activation in chronic fatigue syndrome. Muscle & Nerve, 2003; sep, S157.

LAATSTE WOORD

Een laatste (dank) woord aan alle reisgenoten. Het voltooien van een proefschrift is het volbrengen van een lange avontuurlijke reis. Een reis die zeer afwisselend is verlopen. Soms over geplaveide wegen, soms over nauwelijks begaanbare paden, maar immer door afwisselende landschappen met weidse vergezichten. Een reis met veel variatie en onverwachte gebeurtenissen. Daarbij altijd de ontmoeting met vele reisgenoten, bestaande uit korte ontmoetingen en anderen reisden weer langer mee.

Gaarne wil ik mijn dank betuigen aan alle reisgenoten die met mij deze reis hebben beleefd en doorstaan.

Een eerste woord aan alle deelnemende patiënten. Van heinde en verre reisde u naar Nijmegen om deel te nemen aan het onderzoek. Het belangenloos beschikbaar stellen van uw tijd, inzet en openhartigheid heeft dit onderzoek doen slagen! Met veel genoegen denk ik aan deze ontmoetingen terug.

Daarnaast het basisteam dat met elkaar deze reis heeft beleefd:

De drie promotores, "de hooggeleerde jongens", Gijs Bleijenberg, Baziel van Engelen en Machiel Zwarts. Drie kapiteins op een schip op ontdekkingsreis was soms lastig, maar gaf ook aanleiding tot diepgaande discussies en het opstellen van kritische (onderzoeks) vragen.

Met collega onderzoekers Maartje Schillings en Sieberen van der Werf, aan het begin van de reis, was de bemanning compleet. Jarenlang hebben we als basisteam maandelijks overleg gehad met betrekking tot het ontrafelen van vermoeidheid bij patiënten met verschillende neuromusculaire aandoeningen. Reisplannen werden besproken, logistieke zaken geregeld en als het nodig was werd de route gewijzigd en/of aangepast. Ons maandelijks overleg gaf voldoende stof voor uitvoerige discussies zodat uiteindelijk een voeten-op-tafel-discussie in het leven werd geroepen. Helaas werd de kurk niet uit de fles gehaald, misschien waren de resultaten dan heel anders geworden!

Met promotores en onderzoekers uit verschillende disciplines (psychologie, neurologie, klinische neurofysiologie, F.C. Donders centre en revalidatie geneeskunde) vormden we een waar multi-disciplinair team!

Collega's van verschillende afdelingen, met name noem ik de afdeling Medische Psychologie, het Nijmeegs Kenniscentrum Chronische Vermoeidheid en de afdeling Klinische Neurofysiologie, dank ik voor de steun tijdens deze reis, de gezelligheid en hulp bij het een of ander.

De reisgenoten die mij geweldig geholpen hebben bij de accurate dataverzameling en dataverwerking: ik noem Tiny Fasotti, Danielle van Hout, Henny Janssen, Carel Kruip, Jetske Oostelbosch en Harmen Vissers.

Daar waren altijd "de meisjes" van het secretariaat, Nancy, Helma en Jacintha. Altijd bereid om mijn reisverhalen aan te horen, brieven of faxen te verzenden, tot en met de verzending van deze boekjes.

Ria te Winkel-Slotboom heeft me altijd geweldig geholpen, van stickers plakken in de 1100 screeningsboekjes (de klokken gingen luiden bij Jacob!), logistiek van actometers, patiëntnummering, dataverwerking, tot en met een laatste hand aan dit proefschrift!
Collega onderzoekers en kamergenoten dank ik voor het aanhoren van mijn dagelijkse beslommeringen, discussies over statistische analyses en vooral voor de gezelligheid en voor de vele lunches samen. Elke week begon met de briefing op maandagochtend om 9.00 uur. Kort voor dit wekelijks gebeuren was een ieder naarstig op zoek naar een vraag, een onbegrijpelijke statistische analyse of ander probleem. Mogelijk verhoogt dit de creativiteit onder wetenschappelijk onderzoekers!

Tot slot een woord aan enkele dierbaren. Marita en Henk, jullie reisden mee met al mijn avonturen. Jullie gaven me twee geweldige neefjes, Koen en Sander, door jullie blijf ik jong en in de (hedendaagse) tijd op al mijn reizen!

Het laatste woord is aan mijn ouders. Pap en Mam, jullie hebben als thuishaven en als redders aan de wal mijn levensreis gevolgd en gesteund. We hebben ervaren dat het oplopen van averij bij deze reis kan horen. Maar we hebben ook geleerd dat deze ballast kan worden omgezet in bagage. Met deze bagage zet ik mijn reis voort!

Arnhem, september 2006
J.S.K.

CURRICULUM VITAE

Joke S. Kalkman werd op 27 december 1966 in Den Helder geboren. Hier in de Kop van Noord-Holland werd de lagere school en middelbare school bezocht. Voor een combinatie van een revalidatiebehandeling en universitaire opleiding werd naar Nijmegen afgereisd. Deze combinatie maakte het haar mogelijk om psychologie en geneeskunde zowel theoretisch te bestuderen als praktisch te toetsen. In 1994 voltooide zij haar universitaire opleidingen. Vervolgens was zij werkzaam in het revalidatiecentrum Het Roessingh in Enschede, het Academisch Ziekenhuis Utrecht in samenwerking met de Columbia University in New York (USA), de Grift Gelders Centrum voor Verslavingszorg en het Universitair Medisch Centrum St. Radboud in Nijmegen. In het UMC St. Radboud werd het onderzoek waarvan dit proefschrift het resultaat is uitgevoerd.