Cognitive Behavioral Therapy in FSHD

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Zusammenfassung

Facioscapulohumeral muscular dystrophy (FSHD) and myotonic dystrophy type 1 (MD1) are both chronic, slowly progressive muscular dystrophies. Two randomized controlled trials showed that cognitive behavioral therapy (CBT) is able to decrease experienced fatigue in FSHD and MD1, this effect was still present at follow-up. In FSHD, MRI measurements showed a deceleration of the increase of fatty infiltration of the upper leg muscles. In the future, CBT should be implemented as part of rehabilitation treatment for patients with FSHD or DM1 and chronic fatigue. A first step of implementation of CBT into rehabilitation treatment was made in 2018 at the rehabilitation center "Hoher Meißner" in Bad Sooden-Allendorf, Germany. After implementing a CBT-based group treatment, a reduction of fatigue symptoms was measured in patients.

Keywords: Facioscapular muscular dystrophy, Myotonic dystrophy type 1, Cognitive behavioural Therapy, Rehabilitation

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Introduction and case history

Mr. C is a 58-year old man with FSHD diagnosed at the age of 22. Apart from this muscle disease, he has always been healthy. He has worked fulltime most of his life but, since five years, he has been declared unfit for work. He used to live in a home with a garden, together with his wife. Because he was not able to walk stairs anymore, they were forced to move to an apartment with a small balcony. Since gardening was his hobby, he lost his main activity which he replaced by taking a nap every afternoon. At night, he is frequently awake and in the morning he is already fatigued from the beginning of the day. His wife wants him to go with her to family and friends, but he is reluctant to do so because he hates talking about his disease and getting all sorts of well-meant advice. He is afraid that exercise might damage his muscles, as he regularly experiences muscle pain after physical activity. As a consequence, he has stopped his daily cycling sessions on a home trainer. His maximal walking distance has decreased to just a couple of hundred meters, which makes him increasingly home-bound. Altogether, his changing condition and circumstances have drawn him into a vicious circle of physical inactivity and fatigue, with a great impact on his quality of life.

For patients with facioscapulohumeral muscular dystrophy (FSHD) and Myotonic Dystrophy type 1 (MD1), medical involvement often stops after receiving the diagnosis but, from their perspective, the need for medical attention has just begun. Patients, clinicians and researchers are searching for a curative treatment but, meanwhile, care for the consequences of the disease is just as important, especially in the short turn. Many patients with FSHD and MD1 try to keep up their participation in social life and work. Citing a patient with FSHD: "You just want to live your life like everyone else. That should be the aim of medical research". Yet, being physically active is difficult for patients due to muscle weakness. The resulting reduction in aerobic capacity further restricts social participation. Moreover, more than 60% of the patients with FSHD and MD1 are severely fatigued [16]. In the past, fatigue in FSHD and MD1 have received little attention as it was regarded as an untreatable problem patients "just had to live with".

Facioscapulohumeral muscular dystrophy (FSHD)

FSHD is the third-most common muscular dystrophy. The estimated prevalence is up to one in 8,000 persons [4]. FSHD is an autosomal dominant disease. It is associated with subtelomeric contraction of the D4Z4 repeat region at chromosome 4q, with loss of tandem repeat units and toxic expression of the DUX4 gene in muscle cells [19]. In unaffected individuals, the D4Z4 array consists of 11 to 150 repeats, whereas FSHD patients have only 1 to 10 repeats. In general, the disorder is more severe in patients with lower numbers of repeats.

FSHD derives its name from the muscle groups that are affected first: facial and shoulder girdle muscles. While the disease progresses, humeral, abdominal, pelvic girdle and foot dorsiflexor muscles often become involved as well [26].

Lower abdominal muscles are weaker than the upper abdominal muscles, causing a 'Beevor's sign', a physical finding typical for FSHD [29].

The heart is not affected in most cases, although asymptomatic arrhythmias and conduction defects have

Kognitive Verhaltenstherapie bei FSHD

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Abstract

Fazioskapulohumerale Muskeldystrophie (FSHD) und Myotone Dystrophie Typ 1 (MD1) sind chronische, langsam fortschreitende Muskeldystrophien. Zwei randomisiert-kontrollierte Studien belegten, dass kognitive Verhaltenstherapie die wahrgenommene Fatigue in FSHD und MD1 reduzieren kann und dieser Effekt auch in der Nachuntersuchung fortbesteht. Ferner zeigten MRT- Messungen bei FSHD-Betroffenen eine Verzögerung der Zunahme der Fett-Infiltrierung in der Oberschenkelmuskulatur. Kognitive Verhaltenstherapie sollte daher zukünftig als Bestandteil der Rehabilitationsbehandlung von Patienten mit FSHD oder MD1 und Fatigue implementiert werden. Ein erster Schritt in Richtung Implementation kognitiver Verhaltenstherapie in die Rehabilitationsbehandlung wurde 2018 in der Klinik Hoher Meißner in Bad Sooden-Allendorf, Deutschland, unternommen. Mit der Etablierung einer kognitiv-verhaltenstherapeutisch orientierten Gruppenbehandlung konnte eine Milderung der Fatigue-Symptome bei betroffenen Rehabilitationspatienten erzielt werden.

Schlüsselwörter: Fazioskapulohumerale Muskeldystrophie, Myotone Dystrophie Typ 1, kognitive Verhaltenstherapie, Rehabilitation

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been described [10]. The median age of onset is around 17 years, but the onset of clinical symptoms varies from infancy to the seventh decade. Approximately 20 % of patients eventually become wheelchair-dependent. Most of the patients have a normal life expectancy [32].

Myotonic Dystrophy (MD1)

Myotonic dystrophy is the second-most common muscular dystrophy. There are two major forms: MD1, also known as Steinert's disease, and MD2, a multisystem disease, also known as proximal myotonic myop¬athy (PROMM). In this article, we will limit the discussion to MD1, which is more frequent.

MD1 is divided into congenital, classical and minimal phenotypes according to the age of the symptom onset and disease severity. The prevalence of MD1 is approximately one in 8,000 in the general population [20]. MD1 is an autosomal-dominant disorder, of which the molecular basis is expansion of an unstable repeat sequence in a non-coding part of the dys-trophia myotonica protein kinase (DMPK) gene on chromosome 19. The repeat expansion enlarges with each generation, which leads to earlier onset and increased severity of symptoms with each affected generation, a phenomenon which is known as "anticipation" [11].

MD1 is clinically characterized by muscle weakness of the distal limbs, progressing to the proximal limbs with gradual occurrence of myotonia (delayed relaxation after muscle contraction). Weakness occurs most frequently in facial muscles, the distal muscles of the forearm, and the ankle dorsiflexors, with onset of symptoms in the second, third or fourth decade. Associated findings include muscle pain, cognitive and psychological changes, cataracts, cardiac conduction defects and endocrine disorders [6; 17; 20]. Excessive daytime sleepiness is found in about one-third of patients [3, 24].

The diagnosis can be suspected clinically by a positive family history and by identifying the symptoms mentioned above. Specific genetic testing to demonstrate the presence of an expanded CTG repeat in the DMPK gene is the gold standard for the diagnosis of MD1 [20]. There is no disease-modifying therapy available for the treatment of MD1. Therefore, treatment is symptomatic.

Fatigue

The Departments of Neurology, Rehabilitation and Pediatrics of the Radboud University Medical Center together with the Expert Center for Chronic Fatigue collaborate in the Center of Expertise for Muscular Dystrophy and have worked together in research and patient care in muscular dystrophy for over 20 years. One of the research successes is the result of cross-sectional and longitudinal research on experienced fatigue In FSHD and MD1. Cross-sectional research showed that experienced fatigue is a frequent as well as a relevant problem for patients with FSHD and MD1.

Based on longitudinal data, a model of perpetuating factors of experienced fatigue in patients with FSHD and MD1 was developed **(Figure 1)** [16]. Muscle weakness, the key feature of FSHD and MD1 and the result of fatty infiltration of the skeletal muscles, appeared to contribute only indirectly to experienced fatigue. However, muscle weakness leads to physical inactivity, the most important perpetuating factor of experienced fatigue. Sleep disorders and pain are the other proven perpetuating factors of experienced fatigue.

FSHD and MD1 have a strong impact on psychosocial functioning as patients have to periodically re-adapt their daily life activities to living with a progressive illness. Illness cognitions and coping style influence the choice and level of activities and, hence, quality of life.

Because a cognitive-behavioral approach influencing illness cognitions and coping strategies has been proven successful for chronic fatigue syndrome [25] and post-cancer fatigue [7], it was expected to be efficacious for chronic fatigue in patients with FSHD and MD1 as well.

From 2010 till 2014 the FACTS-2-FSHD study (acronym for Fitness And Cognitive behavioral TherapieS for Fatigue and ACTivitieS in FSHD) which is the first model-based randomized clinical trial that evaluates the effects of aerobic exercise training (AET) and cognitive behavioral therapy (CBT) on chronic fatigue in patients with FSHD, was conducted [13, 36]. These interventions are based on the above-mentioned model of chronic fatigue. The primary objective of this study was to evalu-

ate the effect of both interventions on chronic fatigue in patients with FSHD as assessed with the subscale fatigue of the Checklist Individual Strength. The secondary objective was to evaluate the effects of each intervention on the known perpetuating factors of chronic fatigue in FSHD based on secondary outcome measures covering all domains of the International Classification of Functioning, Disability and Health (ICF). In addition, it was aimed to find clinically useful MRI biomarkers of disease progression and response to therapy in patients with FSHD [13].

CBT in this study was composed of six modules directed at the proven and presumed perpetuating factors of experienced fatigue and their related (unhelpful) cognitions in FSHD. The modules focused on: unhelpful coping strategies; unhelpful cognitions about fatigue; activity, pain or other symptoms; catastrophic thoughts about fatigue; sleep disturbances; physical inactivity or dysregulation of physical activity; and a discrepancy between expected and actual social support and interactions. Additionally, reducing restrictions in social participation was an important objective of the CBT.

Fifty-seven ambulant patients with FSHD type 1 and severe chronic fatigue were randomly allocated to AET, CBT, or usual care (UC). Following treatment, the CBT (25 participants) intervention group had significantly less fatigue relative to the UC group (24 participants), with a difference of -13.3 for CBT (95 % CI: -16.5 to -10.2) on the CIS-fatigue. These beneficial effects lasted through 12-week follow-up, with a difference of -10.2 for CBT (95 % CI -14.0 to -6.3). Post-treatment, 19 participants in the CBT group (76 %) no longer had scores indicative of severe fatigue. The number needed to treat (NNT) for CBT was 1.3 (95 % CI 1.1–1.7) with an absolute risk reduction of 76 % (95 % CI 59–93 %). In the CBT group, all known fatigue-perpetuating factors (with the exception of pain) were positively modified, including a higher level of social participation. The increase in registered physical activity in both groups and the improvement in social participation following CBT were still present at follow-up. Almost 80 % of the CBT participants continued their adjusted level of activity once the study had ended. The median number of CBT sessions was only five. It was concluded that CBT is able to ameliorate chronic fatigue in patients with FSHD.

Quantitative T2-MRI (qT2-MRI) and fat-suppressed T2-MRI images of the thigh were obtained at baseline and follow-up in 31 patients who were included in the FACTS-2-FSHD study, of whom 13 received usual care (UC) and nine CBT. In the UC group the fatty infiltration in the affected muscles progressed on average with 6.7 % per year. Progression occurred on average in all muscles except in the gastrocnemius, sartorius and vastus lateralis. Overall, the adductor magnus showed the largest progression. This rate was significantly lowered by 1.7 % per year in the CBT group (CBT – UC, p<0.01). In the CBT group, fewer muscles developed edema than was observed in the UC group. It was concluded that CBT is able to slow down the progression of fatty replacement of muscle tissue in FSHD.

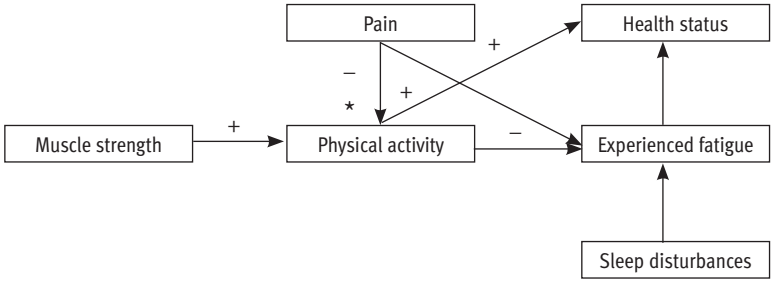

Figure 1 Model of perpetuating factors of fatigue for patients with FSHD (Source: Adapted from [18])

From 2014 till 2016, a multicentre, single-blind, randomized trial was conducted at four neuromuscular referral centres with experience in treating patients with MD1 located in Paris (France), Munich (Germany), Nijmegen (Netherlands), and Newcastle (UK). Eligible participants were patients aged 18 years and older with a confirmed genetic diagnosis of MD1, who were severely fatigued (i.e., a score of ≥35 on the checklist individual strength, subscale fatigue). In total 255 patients were randomly assigned to CBT plus standard care and optional graded exercise or standard care alone. CBT focused on addressing reduced patient initiative, increasing physical activity, optimizing social interaction, regulating sleep–wake patterns, coping with pain, and addressing beliefs about fatigue and MD1. CBT was delivered over a 10-month period in 10–14 sessions. A graded exercise module could be added to CBT in Nijmegen and Newcastle. The primary outcome was the 10-month change from baseline in scores on the DM1-Activ-c.

The DM1-Activ-c score increased from a mean (SD) of 61 ± 22 (17 ± 35) points at baseline to 63 ± 92 (17 ± 41) at month 10 in the CBT group (adjusted mean difference 1 ± 53, 95 % CI -0 ± 14 to 3 ± 20), and decreased from 63 ± 00 (17 ± 35) to 60 ± 79 (18 ± 49) in the standard care group (-2 ± 02, -4 ± 02 to -0 ± 01), with a mean difference between groups of 3 ± 27 points (95 % CI 0 ± 93 to 5.62, p=0.007). 244 adverse events occurred in 65 (51 %) patients in the CBT group and 155 in 63 (50 %) patients in the standard care alone group, the most common of which were falls (155 events in 40 [31 %] patients in the CBT group and 71 in 33 [26 %] patients in the standard care alone group). 24 serious adverse events were recorded in 19 (15 %) patients in the CBT group and 23 in 15 (12 %) patients in the standard care alone group, the most common of which were gastrointestinal and cardiac.

Mr. C, a 58-year old man with facioscapulohumeral dystrophy (FSHD) who was briefly introduced in the introduction of this article, was encouraged by his wife to take part in the FACTS-2-FSHD study, hoping to achieve a reduction of his fatigue. He hoped to be randomized to aerobic exercise training to resume his cycling exercises. He had given up those exercises a couple of years ago for fear of further deterioration of his muscle strength. However, in the study he was randomized to cognitive behavioral therapy (CBT). Initially he was disappointed, as he did not really want to talk to a psychologist about his muscle disease and the burden of his disease. During the study, he received nine sessions of CBT. In the beginning, he was skeptical about this treatment, and therefore did not expect CBT to have any effect. He regarded his experienced fatigue as an untreatable problem. Several measurements that were conducted during the first treatment session with the psychologist showed that the CBT should be directed at unhelpful thoughts and beliefs about fatigue, improper coping strategies, sleep disturbances, physical inactivity and unhelpful social interactions. After nine sessions of CBT and homework assignments, his physical activity had increased substantially. Together with his partner, he went out on an electric bike again to visit his family and friends. He was no longer afraid of muscle damage from physical activity because he noticed that he felt more fit by being physically active. He resumed his gardening activities, this time in the communal garden of the apartment complex where he lived. He no longer slept during lunchtime, so the quality of sleep at night became better. He was not seriously fatigued any more. His mental and physical capacity increased, and there was room for new activities. A few weeks after the end of the CBT, he started a new job.

The patient with FSHD described in the case study showed an improvement in all domains of the International Classification of Functioning, Disability and Health after only nine sessions of CBT. Not only did he experience a lower level of fatigue and an improvement in sleep quality, he also became more physically active. He performed gardening activities again, his social contacts increased and he started a new job. CBT broke the downward spiral of physical inactivity, experienced fatigue and social participation restrictions.

He became physically active in daily life, and social participation became possible again.

The case study illustrates the general conclusion of the two RCTs previously described: CBT is able to reduce severe fatigue in patients with FSHD and MD1 and improve social participation, by increasing physical activity and changing all relevant fatigue perpetuating factors. Surprisingly, a deceleration of fatty replacement of muscle tissue in the thigh muscles was observed after CBT in FSHD.

Possible explanations for effects: physically active lifestyle versus physical exercise

Physical inactivity

After CBT, the level of physical activity in daily life in patients with FSHD and MD1 increased and remained high compared with the control group, even after the follow-up periods. The increase in physical activity in everyday life appears to play an important role in the positive effect of both interventions on the level of fatigue. Based on the model of perpetuating factors of fatigue and additional research, it is known that in FSHD and MD1 the degree of fatigue is not correlated with the severity of muscle weakness [16]. Apparently, this fatigue seems more a result of unintentional unhelpful behavior associated with the disease rather than the result of muscle weakness itself. Conversely, experienced fatigue often leads to unhelpful cognitions and behavior that, in turn, further increase the level of fatigue.

During CBT, a reliable increase in physical activity is an important part of the treatment: the module 'physical-inactivity or a high dysregulation of activity' was applied in each participant.

The recommendations on physical activity for the healthy population have been prescribed in the Dutch Standard for Healthy Exercise (Nederlandse Norm Gezond Bewegen; NNGB). This standard aims at a physically active lifestyle and comprises a total of 30 minutes of exercise of moderate intensity (at a slightly higher heart and respiration rate than usual) of at least 4.0 MET a day, in blocks of at least 10 minutes at least five days a week.

The MET value or the metabolic equivalent is a unit of measurement within physiology expressing the amount of energy for a certain physical effort compared with the amount of energy required at rest. One MET corresponds to the resting metabolic rate, the amount of energy consumed during inactivity. One MET is equivalent to 3.5 ml of oxygen per kg of body weight per minute. The NNGB leads to a total duration of 150 minutes of physical activity per week of 4.0 MET, which implies a total increase of 450 MET per week compared to a physically inactive lifestyle. Physical activity within the NNGB includes not only sports activities but also daily-life activities such as household activities, cycling or walking the dog.

For physical exercise, the Dutch government has issued a standard for physical fitness. This standard is aimed primarily at maintaining aerobic capacity through physical exercise and requires intense physical activity of at least 6.0 MET for at least 20 minutes and at least three times a week. Although the intensity is higher than in the NNGB, the total length and the increase in MET per week is less, namely 300 MET. Thus, one can still have a physically inactive or sedentary lifestyle, in spite of meeting the standard for physical fitness. In other

words, the NNGB leads to a higher level of physical activity than the Dutch standard for physical fitness.

The Dutch standard for physical fitness and the NNGB are defined only for healthy adults and for healthy elderly. The minimum standard for patients with a chronic disease, including FSHD and MD1, has not yet been defined. The NNGB not only leads to a higher level of physical activity; this standard is probably also more feasible for patients with FSHD and MD1, because daily-life activities are included. In other progressive neurological diseases, such as Parkinson's disease, there is already growing evidence for a positive effect of decreasing the sedentary time [34]. The question now arises whether physical exercise of minimum intensity and an increase in aerobic capacity are really necessary for the treatment of fatigue in patients with FSHD and MD1. Would an increase in physical activity of moderate intensity and of sufficient duration, i.e. a physically active lifestyle, not be much more relevant?

Cognitive behavioral therapy

FSHD and MD1 are more than impaired muscle function

In the RCTs, CBT was focsed on the individual person with FSHD or MD1. In the longitudinal study in which the model of perpetuating factors of experienced fatigue has been developed, only a limited number of possible perpetuating factors could be explored [34]. The sample size was too small to reliably test more factors. Therefore, one or more of the presumed perpetuating factors of experienced fatigue (discrepancy in the level of perceived social support, unhelpful illness cognitions and limited social and mental activities) could also be perpetuating factors of experienced fatigue in patients with FSHD and MD1. For example, unhelpful illness cognitions are a known perpetuating factor of experienced fatigue in multiple sclerosis and in chronic fatigue syndrome [35]. As an essential part of CBT, unhelpful cognitions can be changed into helpful thoughts using Socratic dialogues to increase patients' autonomy and self-efficacy.

Although increasing the amount of physical activity is an essential part of CBT for fatigue in FSHD and MD1, both scientists and clinicians are astonished about its beneficial effect. "Is fatigue all in the mind?" and "How can a psychological treatment achieve an effect at a muscular level?" are frequently asked questions. The answer to these questions is that a part of the solution is, in fact, literally "in the mind." Psychological factors, such as illness cognitions, coping style and level of acceptance of the disease are known to be strongly correlated with the degree of social participation in patients with a muscle disease, including FSHD and MD1 [8]. It is noteworthy that these correlations, comparable with the level of experienced fatigue, are relatively independent of the degree of physical impairments. This is also called the

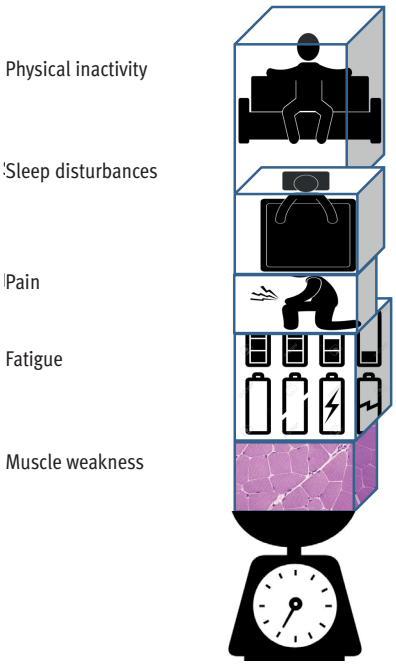

Figure 2: The imaginative tower of experienced burden of disease in patients with facioscapulohumeral dystrophy (FSHD)

FSHD is more than impaired muscle function. A large part of the experienced burden of disease consists of the proven perpetuating factors of fatigue. Not every factor carries equal weight. Experienced fatigue and physical inactivity constitute the main part of the disease burden. The figure is a visual representation of the results of the study by Johnson et al. [15].

"disability paradox:" having physical impairments has little influence on the degree of social participation.

This paradox can be explained by the perceived burden of disease in patients with FSHD and MD1 **(Figure 2)**. As shown in Figure 2, muscle weakness is not only just an indirect perpetuating factor of experienced fatigue, it also constitutes a relatively small part of the experienced burden of disease. Fatigue, pain, sleep disorders and physical inactivity determine the majority of the experienced burden of disease in FSHD and MD1. This implies that psychological interventions are not only able to improve the level of experienced fatigue, but can also improve the degree of social participation and mood of patients with a muscle disease, even when there is progression of the disease [1].

The disability paradox seems to explain part of the large observed effects of CBT. Psychological well-being improved after CBT, as measured by the Brief Symptom Inventory [5] (unpublished data), and the level of social participation increased.

Effects at the muscular level: epigenetics and/or anti-inflammatory effects?

CBT showed to slow down the progression of fatty replacement of muscle tissue in FSHD. This raises the

question: "How is it possible that an increase in physical activity causes a beneficial effect at the muscular level?" Epigenetics and the inflammation theory can possibly offer an explanation.

Epigenetics

FSHD is a genetic disorder. More than 95 % of cases of FSHD are associated with the absence of certain pieces of DNA at the end of chromosome 4 (genetic location: 4q35), the so-called D4Z4 deletion. This results in expression of the harmful DUX4 gene and production of a toxic protein (DUX4) that causes dystrophy (fatty replacement) of the skeletal muscles [27]. The conversion of DNA into functional products for the cell, such as proteins, is dependent on both the DNA code itself (genetics) as well as on factors that may affect the activity of genes (gene expression), so-called epigenetic factors [14]. Epigenetic phenomena determine the "open" or "closed" state of parts of the genome and, thus, control the "on" or "off" position of genes. This can take place by means of changes in methylation, RNA molecules (intermediates between DNA and protein), or by the so-called histone proteins that are involved in the packing (and hence access) of the DNA in the chromosomes. Individuals genetically determined to have FSHD, show a wide range of clinical severity, age of onset, and rate of disease progression, including some who remain asymptomatic throughout their lives. This variability suggests that the disease has a strong epigenetic component [14]. In FSHD patients, the degree of methylation of the DNA influenced by epigenetic factors plays an important role. Sometimes a small molecule group is added to the DNA, a so-called methyl group, which carries additional information. FSHD patients with a D4Z4 deletion (FSHD-1) show a decreased methylation of the D4Z4 region on the chromosomes 4q and 10q.

However, the degree of methylation is not already determined at birth. It varies between persons and may change under the influence of environmental factors during one's lifetime.

Epigenetic factors ensure that the genetic defect in different people, even within families, can be expressed differently [22]. In recent research, the difference in severity of the disease within families with FSHD is, among other phenomena, attributed to epigenetic factors [33].

An increase in physical activity and/or physical exercise can cause changes in the DNA methylation of healthy persons [2]. It is possible that a physically active lifestyle is an epigenetic factor for FSHD and can slow down the progression of fatty replacement of muscle tissue by changes in DNA methylation. It is not a coincidence that the perpetuating factors of fatigue, i.e. physical inactivity, sleep disorders and pain, are known epigenetic factors [30]. The degree of methylation can be different for every individual cell under the influence of epigenetic factors. This could be an explanation for the differences in effect on the fatty replacement between different muscles of patients with FSHD after CBT, as measured by quantitative magnetic resonance imaging (MRI) [13]. To conclude, the first hypothesis is that CBT influences the fatty replacement of muscle tissue by modifying epigenetic mechanisms.

Exercise is medicine

Nevertheless, the scientific acceptance of CBT as medicine in FSHD and MD1 is still difficult. Although the effect of CBT was examined "lege artis" and based on a theoretical model of perpetuating factors of experienced fatigue, there is still uncertainty (and even scepsis) with regard to the underlying mechanism.

The acceptance of functionally targeted interventions can possibly be accelerated by providing more evidence for underlying mechanisms through basic research. However, the biggest challenge is to get the scientific and clinical world moving forward. This requires a societal change. A change in lifestyle requires a greater effort from patients and practitioners than taking or prescribing a drug. And even medication adherence is limited [9]. In CBT, therapy sessions are usually structured by a collaboratively agreed-on agenda. Homework sessions encourage active participation. Research has shown that a patient-centered approach improves treatment adherence in chronic patients and also improves job satisfaction in health professionals [21].

Recently, a new definition of health has been introduced by Huber, in which health is no longer described simply as the absence of disease [12]. Policy makers, researchers and clinicians have always had a rather narrow, biomedical interpretation of health, paying particular attention to bodily functions, whereas patients themselves often strived for a broader definition for the concept of health. The new, more positive definition of health is "the ability to adapt and to self-manage, in the face of social, mental and physical challenges of life." This means that patients with FSHD and MD1, despite his or her muscle weakness, can still be healthy if there is a balance in the demands and personal aims of everyday life and if (s)he experiences sufficient self-control and meaning in life. Through an increase in autonomy and active participation, which is the aim of both CBT, the perceived health status can improve further. Although most physicians still tend to adhere to a narrow, biomedical definition of health, rehabilitation medicine has already embraced a more functionally oriented definition of health since its existence. Therefore, Huber's definition of health corresponds well with the focus of rehabilitation medicine to promote autonomy and independence in human beings independent of their disease status.

CBT: part of rehabilitation

The beneficial effect of CBT was not only larger than expected, but also applicable to more domains than expected. In the future, CBT should be implemented as part of rehabilitation treatment for patients with FSHD or DM1 and chronic fatigue.

A first step of implementation of CBT into rehabilitation treatment was made 2018 at the rehabilitation center „Hoher Meißner“ in Bad Sooden-Allendorf, Germany.

According to the recommendations of Voet et al. [36] a CBT-based treatment of chronic fatigue for FSHD and MD1 patients was offered within a specialized inpatient rehabilitation. Due to the specification of the rehabilitation setting with a duration of approximately three weeks and a multitude of patients with chronic fatigue symptoms, an adapted treatment program was created. To enable every rehabilitation patient with chronic fatigue to take part in the CBT treatment, a group setting concept was chosen. This group program comprised of three group sessions during rehabilitation, whereas two meetings took part during the first week and a final meeting in the last week before discharge of the participants. A CBT break during the second week of rehabilitation intended to give participants the chance to practice helpful cognitions and a physical active lifestyle in order to become aware of its usefulness for handling chronic fatigue symptoms. Within the intensive rehabilitation set patients receive an individually tailored treatment program (e. g. physiotherapy, occupational therapy, speech therapy) for stimulating physical activity. Furthermore, the structure of the rehabilitation building demands patients to become active in a number of therapies at different locations and use several ways to move from or to the room, restaurant etc..

The six important modules mentioned by Voet and colleagues [36] (i.e., “insufficient coping with the disease; dysfunctional cognitions regarding fatigue, activity, pain, or other symptoms; fatigue catastrophizing; dysregulation of sleep or activity; poor social support; and negative social interactions”) were profoundly addressed during the group program.

Aims of the group treatment include the improvement of comprehension and consciousness of fatigue symptoms as well as the encouragement of acceptance in order to achieve functional coping with the muscular disease. Relationships to other aspects such as insufficient sleep and dysfunctional handling of chronic pain are also addressed. A further aim is the acquisition of functional coping strategies with a focus on the importance of regular activity and helpful cognitions for a functional personal attitude to enable participants to continue an active lifestyle under home circumstances after rehabilitation.

Methodologically, acquisition of knowledge concerning a definition of fatigue and its special quality in neuromuscular diseases as well as psychoeducation in the handling of pain and impaired sleep are targeted aims of this group treatment. Furthermore, participants are sensitized towards the positive aspect of continuous activity as helpful lifestyle. Against this background, functional cognitions and attitudes towards an improved dealing with fatigue symptoms in daily life and, in particular, regular activity are acquired. Group discussion is further used for exchange of experiences among participants to find solutions for daily activities under the individual circumstances of patients at their home. Experiences during rehabilitation with an intensive treatment and circumstances demanding daily activity are discussed with regard to a change in reported fatigue symptoms. Improvements in assessments of physiotherapists, occupational therapists and speech therapists from the beginning to the end of the rehabilitation support the psychotherapeutic intention. Finally, motivation as well as helpful suggestions for the improvement of activity within daily life of the participants at home are considered.

Clinical experiences during the new treatment show that patients accept and support the group program within the rehabilitation setting. Participants report alleviation of individual doubts about the felt lack of energy and mention relief to now being able to give the misunderstood symptoms a label. Often, patients report to receive information about the concept of fatigue for the very first time. Furthermore, the possibility to exchange experiences with others as well as to develop helpful cognitions concerning fatigue in order to find a better functional handling of its symptoms in their individual daily life was frequently acknowledged.

In a recent observational study, the new treatment group program was evaluated. The German version of the Multidimensional Fatigue Inventory (MFI-20) [28; 31] and an additional adapted questionnaire were used to compare the perceived fatigue of group participants at the begin and at the end of the treatment program as well as 2 to 6 weeks after rehabilitation. The sample comprised of 40 group participants, 52 % females and 48 % males with an average age of 50.1 years. Results of the data analysis show a significant reduction of general fatigue, mental fatigue, and physical fatigue symptoms at the end of the rehabilitation. Also, a significant increase in motivation for activity was registered. Furthermore, the reduction of general fatigue symptoms persisted after rehabilitation. Due to the lack of a control group the question of causation of these positive effects by the specific treatment program or by the overall rehabilitation process cannot be sufficiently clarified. In order to address this, detailed judgements from the group participants were collected. From the individual point of view, all patients evaluated the new group treatment program as being beneficial during rehabilitation.

91% of the participants believed to have received helpful information concerning fatigue and its symptoms during the entire rehabilitation period. Overall, 70% of participants reported a subjective improvement of fatigue burden at the end of the rehabilitation. The subjective degree of fatigue improvement at the end of the rehabilitation amounted to approximately 37%.

To shed light on the question of the individual impact of different therapeutic factors on the achieved reduction of fatigue symptoms, group participants were also asked to estimate the specific contributions of the fatigue group treatment, physiotherapy and occupational therapy, as well as the exchange with other patients towards the overall rehabilitation effects. Patients rated the impact of physiotherapy and occupational therapy as approximately 44.1%, the contribution of the fatigue group as approximately 30.7% and the impact of exchanges with other patients as approximately 24.9% of the overall rehabilitation effect. 93% of the interviewed participants judged the contents of the group treatment to be relevant for themselves and their individual circumstances at home.

Two to six weeks after discharge, group participants reported individual improved handling of fatigue symptoms in their home environment. Approximately 96% of the interviewed participants felt less burdened as well as more able to comprehend fatigue symptoms. Approximately 92% of patients were more conscious for initial physical or mental signs of their individual fatigue symptoms. Around 83% of the patients were more aware of associations with other aspects such as sleep or pain management, and approximately 79% registered an improved overall acceptance of their fatigue. The handling of fatigue symptoms under home circumstances was improved in approximately 67% of the group participants. Furthermore, 92% of the patients reported an increase of their daily activities or to continue established activities at home with more consciousness. Since mental approaches to handling fatigue symptoms are rarely emphasized in customary rehabilitation for neuromuscular diseases, these positive effects seem to have resulted from the CBT-supported rehabilitation program which now targeted also on helpful cognitions and adaptive coping strategies concerning fatigue symptoms.

In summary, it was demonstrated that a reduction of fatigue symptoms can be achieved or enhanced during specific rehabilitation for neuromuscular diseases. The administered CBT-based group treatment for neuromuscular disease patients with fatigue symptoms was regarded by patients as being meaningful, helpful, and relevant for their individual coping process.

Not every rehabilitation center or hospital will have a sufficient number of psychologists qualified in CBT. Implementing CBT as standard care in rehabilitation can therefore be difficult, also because of the costs of a psychological treatment. To solve this problem, the principle of "stepped care" could be applied. Stepped care means that the most effective yet least resource-intensive treatment is delivered to patients first, only "stepping up" to more intensive treatments when clinically required. Step one can be the implementation of CBT techniques such as increasing physical activity through a graded activity program by physical and/or occupational therapists, and help to adhere to regular sleep–wake times and change unhelpful thoughts by rehabilitation physicians [37]. To further optimize the effect of CBT and in the case of psychopathological symptoms, counseling by a psychologist specialized in CBT can be administered as a second step. CBT has to be considered as medicine too. The psychologist will have to prescribe which specific modules have to be followed. Almost always, the dysregulation of physical activity module will be part of the treatment. CBT can also be supported by e-health, for example by using an interactive application, in order to save costs [23].

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Conflict of interest:
Both authors declare that there is no conflict of interest.

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