Clinical Neurophysiology 118 (2007) 292–300

www.elsevier.com/locate/clinph

Experienced and physiological fatigue in neuromuscular disorders

M.L. Schillings [a,d], J.S. Kalkman [b], H.M.H.A. Janssen [a], B.G.M. van Engelen [c,d], G. Bleijenberg [b], M.J. Zwarts [a,d,*]

[a] *Department of Clinical Neurophysiology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands*
[b] *Expert Centre Chronic Fatigue, The Netherlands*
[c] *Department of Neurology, The Netherlands*
[d] *Institute for Fundamental and Clinical Human Movement Sciences (IFKB), The Netherlands*

Accepted 31 October 2006

Abstract

Objective: Fatigue has been described as a typical symptom of 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: Sixty-five facioscapulohumeral dystrophy (FSHD), 79 classical myotonic dystrophy (DM), 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.

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.

Conclusions: 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.

Significance: For the clinician it is important to know that experienced fatigue is part of the clinical spectrum of neuromuscular patients. Besides, the weakness in these patients is aggravated by reduced central activation. Potentially, both problems could be subject of an intervention.

Keywords: Central fatigue; Central activation; Peripheral fatigue; Neuromuscular disorders; Surface EMG

1. Introduction

Fatigue is a typical symptom of neurological diseases (Chaudhuri and Behan, 2004). It is present in more than 60% of patients with a neuromuscular disorder (Kalkman et al., 2002; Paul et al., 2000; Merkies et al., 1999). In Parkinson's disease, more fatigue is associated with less physical activity, worse physical function, and lower functional capacity (Garber and Friedman, 2003). 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 (Chaudhuri

* Corresponding author. Tel.: +31 24 3613973; fax: +31 24 3615097.
E-mail address: M.Zwarts@neuro.umcn.nl (M.J. Zwarts).

1388-2457/$32.00
doi:10.1016/j.clinph.2006.10.018

and Behan, 2004). Krupp and Pollina (1996) have described it to be an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion. The symptom is distinguished from weakness (Krupp and Pollina, 1996) and does not necessarily correlate with signs of physiological fatigue (Iriarte and de Castro, 1998).

Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force (Gandevia, 2001). It is divided into peripheral and central components, a division 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 (MVC), healthy subjects develop both peripheral and central fatigue (Kent-Braun, 1999; Schillings et al., 2003). The occurrence of central fatigue means that central activation worsens during the contraction. However, central activation is suboptimal already at the start of a sustained MVC (Schillings et al., 2003).

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 et al. (1995) have described that increased fatigability inevitably occurs in patients with muscle weakness, regardless of whether the latter is due to a central or a peripheral neurological disorder. Not only (possibly indirect) peripheral changes, but also central changes could be responsible for this. Recently, alterations in the central nervous system in muscle dystrophies have been described (Di Lazzaro et al., 2004; Oliveri et al., 1997; Liepert et al., 2004; D'Angelo and Bresolin, 2001; Mochizuki et al., 2001; Funakoshi et al., 1998; Sigford and Lanham, 1998), 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 (DM), a multisystem disorder.

2. Subjects and methods

2.1. Subjects

Age-matched groups of 65 FSHD-, 79 classical DM-, 73 HMSN-patients and 24 neurologically healthy controls participated in the study (Table 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° were included.

Disease severity was determined with the Medical Research Council grading scale (MRC; 0–5) investigating the strength of the shoulder, forearm, calf and upper leg. In order to characterise the patients, these eight values (both left and right) were averaged (Table 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.

2.2. Experienced fatigue

Just before the start of the physiological protocol, all patients and 16 controls filled out the 4-item abbreviated fatigue questionnaire (AFQ) (Alberts et al., 2001) 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) to evaluate the level of experienced fatigue during the past two weeks.

2.3. Physiological factors of fatigue

2.3.1. Experimental set-up

The experimental design has been used earlier in studies into peripheral and central aspects of fatigue in healthy subjects (Schillings et al., 2003) and in patients with chronic fatigue syndrome (Schillings et al., 2004). It is based on the twitch interpolation technique (Merton, 1954).

Table 1
Details of subject groups

	N_total	Men (%)	Women (%)	Age			Mean MRC			DNA		
				Mean	SD	Range	Mean	SD	Range	Confirmed (%)	Not conf. (%)	Not tested (%)
FSHD	65	58.5	41.5	43.1	10.3	22.5–60.9	3.6	0.8	1.9–5.0	83.1	6.2	10.8
DM	79	55.7	44.3	41.0	9.8	22.5–56.6	3.7	0.8	2.0–5.0	62.0	–	38.0
HMSN	73	41.1	58.9	42.4	9.8	20.0–58.0	3.7	0.9	1.5–5.0	45.2	6.8	47.9
Control	24	50.0	50.0	42.1	13.5	21.7–59.3	5.0	0.0	5.0–5.0	–	–	–