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ScienceDirect

Neuromuscular Disorders 27 (2017) 526–530

www.elsevier.com/locate/nmd

Respiratory function in facioscapulohumeral muscular dystrophy 1

M. Wohlgemuth [a,*], C.G.C. Horlings [a], E.L. van der Kooi [b], H.J. Gilhuis [c], J.C.M. Hendriks [d], S.M. van der Maarel [e], B.G.M. van Engelen [a], Y.F. Heijdra [f], G.W. Padberg [a]

[a] Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Department of Neurology, Medical Center Leeuwarden, Leeuwarden, The Netherlands
[c] Department of Neurology, Reinier de Graaf Group, Delft, The Netherlands
[d] Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands
[e] Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
[f] Department of Pulmonology, Radboud University Medical Center, Nijmegen, The Netherlands

Received 25 July 2016; received in revised form 16 February 2017; accepted 17 March 2017

Abstract

To test the hypothesis that wheelchair dependency and (kypho-)scoliosis are risk factors for developing respiratory insufficiency in facioscapulohumeral muscular dystrophy, we examined 81 patients with facioscapulohumeral muscular dystrophy 1 of varying degrees of severity ranging from ambulatory patients to wheelchair-bound patients. We examined the patients neurologically and by conducting pulmonary function tests: Forced Vital Capacity, Forced Expiratory Volume in 1 second, and static maximal inspiratory and expiratory mouth pressures.

We did not find pulmonary function test abnormalities in ambulant facioscapulohumeral muscular dystrophy patients. Even though none of the patients complained of respiratory dysfunction, mild to severe respiratory insufficiency was found in more than one third of the wheelchair-dependent patients. Maximal inspiratory pressures and maximal expiratory pressures were decreased in most patients, with a trend that maximal expiratory pressures were more affected than maximal inspiratory pressures. Wheelchair-dependent patients with (kypho-)scoliosis showed the most restricted lung function.

Wheelchair-dependent patients with (kypho-)scoliosis are at risk for developing respiratory function impairment. We advise examining this group of facioscapulohumeral muscular dystrophy patients periodically, even in the absence of symptoms of respiratory insufficiency, given its frequency and impact on daily life and the therapeutic consequences.

Keywords: Facioscapulohumeral muscular dystrophy; FSHD1; Respiratory muscles; Pulmonary function

1. Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common hereditary muscular dystrophies. It is a slowly progressive autosomal dominant myopathy with an estimated prevalence of 1 in 8000 [1]. Initially, the facial and shoulder girdle muscles are affected. Over time, the humeral, abdominal, pelvic girdle, and foot extensor muscles can become involved. The dystrophy is characterized by variability in age at onset, variable progression, and an asymmetry in muscle involvement. Approximately 20% of the patients become wheelchair-dependent. An equal percentage remains asymptomatic [2,3].

In most cases FSHD is associated with a contraction of the subtelomeric D4Z4 repeat on chromosome 4q35 (FSHD1). Together with a specific adjacent distal sequence called 4A, this contraction is responsible for the production of a double homeobox transcription factor DUX4 with a toxic gain of function [4]. Patients with a clinical FSHD phenotype without a contraction of D4Z4, but a mutation in SMCHD1 and a 4qA allele, are labeled FSHD2 [5].

Respiratory insufficiency is not a well-recognized feature of FSHD and its frequency is unknown. Respiratory insufficiency requiring non-invasive ventilation is rare in FSHD. In the Dutch population approximately 1% of FSHD1 patients are on assisted (nocturnal) ventilation [6]. Respiratory failure most commonly occurs in infantile cases with wheelchair dependency and small D4Z4 repeat sizes [7,8]. In ambulant FSHD1 patients, mild global respiratory muscle weakness can

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author. Department of Neurology, Elisabeth TweeSteden Hospital, P.O. Box 90151, 5000 LC Tilburg, The Netherlands. Fax: +31 13 5422538.

E-mail address: m.wohlgemuth@etz.nl (M. Wohlgemuth).

http://dx.doi.org/10.1016/j.nmd.2017.03.008
0960-8966/

be found as well [9–11]. Systematic studies of pulmonary function in FSHD have often included less severely affected patients and spinal deformities were often not mentioned [9–14]. Respiratory insufficiency in neuromuscular diseases manifests early as nocturnal hypoventilation. Symptoms of nocturnal hypoventilation include disturbed sleep, morning headaches, daytime fatigue and somnolence. Progressive respiratory muscle weakness may lead to chronic respiratory failure. More frequently, acute respiratory failure can occur due to an upper respiratory tract infection or after general anesthesia and intubation for surgical procedures. Therefore, detecting respiratory insufficiency is important to effectively manage FSHD [15–17]. Based on the data of the study of patients on ventilatory support, we hypothesized that wheelchair dependency and moderate to severe (kypho-)scoliosis are risk factors for respiratory insufficiency [6].

The purpose of the present study is to test this hypothesis by assessing pulmonary function tests in a large group of mildly to moderately affected FSHD1 patients and in a group of wheelchair-bound FSHD1 patients with or without spinal deformities in the absence of symptoms of respiratory insufficiency.

2. Methods

2.1. Patient selection

We selected a cohort of FSHD1 patients by approaching all the participants of our previous trial on albuterol and training [18] (n = 77) and all wheelchair-bound FSHD1 patients from our database (n = 18). Their clinical diagnosis was genetically confirmed as all included patients, or a first degree relative had a D4Z4 deletion at 4q35 with *Eco*RI fragments smaller than 37 kb after double digestion with *Bln*I [2]. In our cohort ambulatory was defined as ability to walk without walking aids. Ankle-foot orthoses were accepted. We excluded 4 participants from the trial with a walking distance of less than 10 meters. In addition 10 patients were excluded because of the presence of pulmonary or cardiovascular disease, the use of sympathicomimetics or the use of beta-blockers as reported by the patients [18]. As a result, 81 patients with a clinical and genetic diagnosis of FSHD1 were included and divided into three groups: ambulatory FSHD1 patients (n = 63), wheelchair-bound patients without (kypho-)scoliosis (n = 10) and wheelchair-dependent patients with (kypho-)scoliosis (n = 8) (Table 1). The protocol was approved by the local CME and informed consent was obtained.

2.2. Neurological and pulmonary examination

The following data were obtained: demographic data (age, sex, weight and length), age of onset of FSHD, age of wheelchair dependency and *Eco*RI fragment size.

Cardiac and pulmonary symptoms, symptoms of nocturnal hypoventilation and symptoms of dysphagia were assessed with a questionnaire (see Appendix S1). Physical examination was done by the first author with special attention to thoracic and spinal deformities, position of the hips, signs of dyspnea and paradoxical breathing. The spine was examined in erect position and when bending forward. (Kypho-)scoliosis was found positive when observing a gibbus. As standard pulmonary function tests (PFTs) have proven unreliable for patients with FSHD, face mask-adjusted devices were used as previously described and validated [19]. Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) were obtained with a Morgan spirometer (type PM2000). FVC was defined as abnormal if it was less than 80% of the predicted value. An FVC between 60% and 80% of the predicted value was considered mild restricted lung disease, 51–60% moderate and below 50% severe [12]. In wheelchair-bound patients, FVC was measured in the sitting and supine positions. A decline in FVC of more than 20% from the sitting to supine position and/or paradoxical abdominal movement is indicative of

Table 1
The mean and standard error of the patients' characteristics and of the pulmonary function tests by group of wheelchair dependency.

Variables	Ambulant				Wheelchair dependency				Wheelchair dependency and (kypho-)scoliosis			
	N	Mean	(SE)	S	N	Mean	(SE)	S	N	Mean	(SE)	S
Characteristics												
FVC (%pred)	63	103.1	(1.9)	a	10	82.3	(4.5)	b	8	56.9	(5.3)	c
Gender (male)[1]	42	66.7	%	a	6	60.0	%	a	5	62.5	%	a
Smoker (yes)[1]	43	68.0	%	a	6	60.0	%	a	2	25.0	%	a
Age at exam (years)	63	38.5	(1.3)	a	10	50.9	(3.2)	b	8	31.0	(3.8)	a
Age at onset (years)	62	19.3	(1.2)	a	9	14.2	(2.9)	a,b	8	8.6	(3.2)	b
Length (cm)	63	179.5	(1.0)	a	10	175.5	(2.5)	a	8	178.6	(3.0)	a
Weight (kg)	63	76.6	(1.6)	a	10	80.0	(3.7)	a	8	75.8	(4.4)	a
*Eco*RI (kb)	59	25.8	(0.7)	a	10	24.0	(1.8)	a	8	16.0	(2.0)	c
Pulmonary functions												
FVC (%pred)	63	103.1	(1.9)	a	10	82.3	(4.5)	b	8	56.9	(5.3)	c
FEV1(%pred)	63	100.8	(2.1)	a	10	80.3	(5.1)	b	8	59.0	(6.0)	c
FEV1/FVC	63	96.0	(1.0)	a	10	95.4	(2.5)	a,b	8	102.1	(2.9)	b
PEmax (%pred)	63	89.4	(2.7)	a	10	60.1	(6.6)	b	8	39.2	(7.8)	c
PImax (%pred)	63	103.2	(3.0)	a	10	66.6	(7.2)	b	8	48.4	(8.4)	b

SE = standard error; S = significance. a,b,c = groups with the same letter indicate not statistically significantly different, using the contrast test of Tukey or (1) the Chi-square test, respectively. %pred = percentage of the predictive value.