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Diaphragmatic dysfunction in Collagen VI myopathies

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Abstract

Collagen VI-related myopathies are hereditary disorders causing progressive restrictive respiratory insufficiency. Specific diaphragm involvement has been suggested by a drop in supine volumes. This pilot study aimed at characterizing the respiratory muscle phenotype in patients with *COL6A1-3* genes mutations. Lung function, blood gases, muscle strength and respiratory mechanics were measured in 7 patients between 2002 and 2012. Patients were classified as *Early-Severe* ($n = 3$), *Moderate-Progressive* ($n = 2$) and *Mild* ($n = 2$) according to clinical disease presentation. Seven patients (aged 6–28) were evaluated. Forced vital capacity distinguished the *Mild* group (>60% predicted) from the two other groups (<50% predicted). This distinction was also possible using the motor function measure scale. Diaphragmatic dysfunction at rest was observed in all the *Early-Severe* and *Moderate-Progressive* patients. During a voluntary sniff maneuver diaphragmatic dysfunction was observed in all patients, as assessed by a negative gastric pressure. All patients had diaphragmatic fatigue assessed by a tension-time index over the threshold of 0.15. Diaphragmatic dysfunction during a maximal voluntary maneuver and diaphragmatic fatigue are constant features in Collagen VI myopathies. These observations can assist the diagnosis and should be taken in account for the clinical management, with the early detection of sleep-disordered breathing.

Keywords: COLVI-related myopathy; Ullrich congenital muscular dystrophy; Bethlem myopathy; Diaphragm; Respiratory function; Motor function measure scale, Whole body muscle magnetic resonance imaging

1. Introduction

Collagen VI (COLVI)-related myopathies, characterized by mutations in the *COL6A1-3* genes, are nowadays recognized as a continuous clinical spectrum going from Bethlem myopathy, the milder form, to Ullrich

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congenital muscular dystrophy (UCMD), the most severe form, with intermediate phenotypes [1]. UCMD, as described for the first time in 1930, leads to a 'sclero-atonic' phenotype characterized by hypotonia, muscle weakness of early onset with axial and proximal joint contractures and hyperelasticity of distal joints [2]. Respiratory impairment usually develops in the first or second decade and is a common cause of death if not treated with ventilatory support. Arrest of motor milestones with no acquisition of walking ability is seen in a subset of patients, but most children are able to walk. Among those, some show a later progression of muscle weakness with loss of ambulation around 10 years of age, and most of them require mechanical ventilation in childhood or young adulthood [3]. Bethlem myopathy, first described in 1976, is characterized by early contractures of finger flexors, wrists, elbows and ankles [4], and usually begins in the first or second decade. Respiratory failure and distal hyperlaxity may be absent or milder than in UCMD. The disease course is usually slow, with a majority of patients remaining ambulatory. However, progression of muscle weakness often occurs in the fifth decade, with about half of the patients needing walking support or a wheelchair. Patients with intermediate forms display a lesser degree of weakness and a longer period of ambulation.

COLVI myopathies emerge as an important group of disorders, somewhat under-recognized until recently, probably because of a difficult diagnostic approach due to a large clinical variability and the overlapping presentation with other muscular disorders. Therefore, many challenges remain to overcome in order to understand the genetic, biochemical and pathophysiological basis [1].

Respiratory muscle involvement varies according to the neuromuscular disorder. Indeed, the diaphragm and expiratory muscles are preferentially affected in Duchenne muscular dystrophy, whereas intercostals muscles are the weakest respiratory muscles in patients with spinal muscular atrophy [5]. In patients with COLVI-related myopathy, a progressive restrictive respiratory insufficiency may be observed [6,7]. Although pulmonary complications are the most important cause of morbidity and mortality in this disorder, data characterizing the precise respiratory muscle involvement are not available and data regarding respiratory function are only recent. We have previously reported the occurrence of a constant drop in the supine forced vital capacity (FVC*sup*) in a large series of patients with early-onset COLVI-related myopathy [8], suggesting a selective diaphragmatic dysfunction [9]. Moreover, the pathogenesis of muscle degeneration in COLVI deficiency was only recently partially clarified [10]. The first animal model, *Col6a1*$^{-/-}$ mice, was fundamental in understanding the cellular pathways involved in these diseases [11]. Interestingly, the diaphragm appeared to be the most affected muscle, with evident signs of necrosis [11]. A latent mitochondrial dysfunction accompanied by ultrastructural alterations of mitochondria and the sarcoplasmic reticulum, resulting in spontaneous apoptosis was found in about one-third of muscle fibers of the mouse model [10]. Reduced contractile strength of the diaphragm and other muscle groups was also reported [10]. However, up to now, no study has assessed specifically the strength of diaphragm and other respiratory muscles in children with these disorders.

The aim of our study was therefore to characterize the respiratory muscle phenotype of patients harboring mutations in one of the COLVI-encoding genes.

2. Materials and methods

2.1. Patients

The charts of all the patients with a genetically confirmed COLVI-related myopathy who were followed at our multidisciplinary neuromuscular clinic between 2002 and 2012 were retrospectively reviewed. Molecular studies and clinical examination data were collected. Complementary data, including motor function measure scale (MFM), whole body muscle magnetic resonance imaging (WBMRI), and skin and muscle biopsy findings were collected when available. Patients were classified in three groups of clinical severity, according to maximal motor ability and progression [12]. Patients who never walked were classified as '*Early-Severe*', those who acquired walking ability but lost it in the course of the disease as '*Moderate-Progressive*' and those ambulatory with no major loss of motor function as '*Mild*' [13]. Scoliosis surgery was decided during a multidisciplinary discussion, according to the current standards of care [14]. Post-surgery pulmonary function tests were performed at least 6 months after fusion surgery. We also collected the use of intermittent positive pressure breathing (IPPB) and the use of trunk orthesis.

Noninvasive ventilation (NIV) was initiated in case of diurnal hypercapnia (arterialized carbon dioxide tension $PaCO_2$ >45 mmHg), or nocturnal hypercapnia (transcutaneous carbon dioxide ($PtcCO_2$) >50 mmHg for at least 2% of night time) and/or if minimal pulse oximetry (SpO_2) was <90% for at least 2% of night time [15,16]. Invasive ventilation was indicated in case of persistent hypercapnia despite a NIV use over 20/24 h.

The study was approved by the Institutional Review Board of the French learned society for respiratory medicine "Société de Pneumologie de Langue Française", and all patients and parents gave their informed consent.

3. Procedures

3.1. Immunohistochemical studies

COLVI immunolabeling in skin fibroblasts was carried out as previously described [12] or using the refined