

Severe Respiratory and Skeletal Muscles Involvement in a Carrier of Dysferlinopathy With Chronic Obstructive Pulmonary Disease

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The natural course of progressive neuromuscular diseases can be complicated by respiratory muscle involvement. In muscular dystrophies such as Duchenne muscular dystrophy and myotonic dystrophy, respiratory muscle involvement is common. In others such as Becker, limb-girdle, and facioscapulo-humeral dystrophies, respiratory muscle involvement is infrequent and generally occurs in the more severe cases. Recently, it was reported that a mutation in the dysferlin gene and/or dysferlin deficiency causes proximal and distal forms of muscular dystrophy, which are known by the term dysferlinopathy. We describe a case of severe weakness of both limb-girdle and respiratory muscles in a patient who was carrier of the dysferlin gene mutation and who also had COPD. We suggest that the systemic inflammatory response of COPD and the dysferlin deficit interact and are responsible for both the skeletal and respiratory muscle impairment. Key words: chronic obstructive pulmonary disease; respiratory failure; muscular dystrophy; dysferlin; dysferlinopathy. [Respir Care 2010;55(8):1091–1093. © 2010 Daedalus Enterprises]

Introduction

Muscular dystrophies are a group of progressive, genetically determined, primary degenerative myopathies characterized by different degrees and distributions of muscle wasting and weakness.¹

In many muscular dystrophies such as Duchenne muscular dystrophy and myotonic dystrophy, respiratory muscle involvement is common. In others such as Becker, limb-girdle, and facioscapulo-humeral dystrophies, respiratory muscle involvement is infrequent and generally occurs in the more severe cases.²

Chronic respiratory failure is an important contributor to morbidity and mortality in progressive neuromuscular disorders,² and these patients often experience acute respiratory failure requiring endotracheal intubation or tracheostomy and mechanical ventilation.³

Recently, dysferlin was identified as the member of a putative muscle-specific repair complex that permits rapid resealing of membranes disrupted by mechanical stress.⁴ A mutation in the dysferlin gene and/or dysferlin deficiency causes proximal and distal muscular dystrophies designated as limb-girdle muscular dystrophy type 2B, Miyoshi myopathy, and anterior-compartment myopathy, which are known by the term dysferlinopathy.⁵ One unclear feature of dysferlinopathy is the heterogeneity of clinical presentation: the same mutation underlies all the clinical presentations in the same pedigree, and the same clinical presentation can be caused by different kinds of mutations.⁶

Inheritance of dysferlinopathy is autosomal recessive, and the onset of disease is usually late in the first decade, but may be in the second or third decade or even in middle age.^{7,8} Some evidence indicates that inflammation contributes to muscle pathology in dysferlinopathy.⁹

Up to now, several studies have reported a prominent muscle inflammatory response in dysferlinopathy patients. In fact, in an animal model of dysferlin deficiency (the mutant mouse strain called SJL), the disease process was initially considered an “inflammatory” form of muscular dystrophy. Inflammatory changes have been also observed in the skeletal muscles of patients with COPD.¹⁰

We describe marked impairment of both skeletal and respiratory muscles in a patient who is a carrier of a heterozygous mutation in the dysferlin gene and also has COPD.

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Table 1. Pulmonary Function Test and Blood Gas Results

	Baseline	After Steroid Therapy	After NIV	At 2-Year Follow-up
FVC (mL)	1,890 (63% predicted)	2,620 (88% predicted)	ND	2,350 (79% predicted)
FEV ₁ (mL)	850 (36%)	1,480 (64% predicted)	ND	1,080 (47% predicted)
FEV ₁ /FVC (% predicted)	45	56	ND	46
MIP (cm H ₂ O)	37	ND	ND	65
MEP (cm H ₂ O)	22	ND	ND	28
pH	7.37	7.44	7.42	7.39
P _{aCO₂} (mm Hg)	59	52	45	43
P _{aO₂} (mm Hg)	58	71	86	80

NIV = noninvasive ventilation

FVC = forced vital capacity

ND = no data collected

MIP = maximum inspiratory pressure

MEP = maximum expiratory pressure

Case Report

In July 2006 a 70-year-old white man was admitted to our institution's pulmonary rehabilitation program because of COPD. His medical history was remarkable for long-standing productive cough and a 3-year history of exercise-induced dyspnea. He had a 30-pack-year history of cigarette smoking but had stopped smoking a few years prior to admission. Ten years prior to this presentation he was diagnosed as having COPD. Two years later he noticed a slowly progressive weakness of the pelvic and shoulder girdle muscles.

His family history was positive for neuromuscular disease. He was married to his first cousin, and was the father of a child affected by Miyoshi myopathy. His recent medical history included 2 admissions to the intensive care unit because of 2 episodes of hypercapnic acute respiratory failure: the first in April 2006, the second in May 2006.

On admission he complained about dyspnea on exercise, weakness, and easy fatigability of the muscles of the shoulder and pelvic girdles.

Physical examination found symmetrical atrophy in the shoulder and pelvic girdle muscles, hyperlordosis, and marked kyphosis. He was hindered when raising his arms, running, and climbing stairs. Gowers sign was positive. Manual muscle testing revealed 3/5 and 2/5 in the left and right triceps, respectively, and 2/5 and 3/5 in the left and right iliopsoas, respectively. His nutritional status, as assessed by body mass index (kg/m²), was 24. In the supine position his abdominal wall retracted paradoxically during the inspiratory phase.

A radiograph showed elevation of both hemidiaphragms during maximal inspiration. Bilateral paresis of the diaphragm was confirmed fluoroscopically. There were no abnormal electrocardiographic findings. A previous muscular biopsy obtained in another hospital showed muscular fibers ranging from 8 μ m to 48 μ m in diameter, and was conclusive for a non-evolutionary myopathy.

Dystrofin, α -sarcoglycan, and calpain-3 immunoblot were all normal for quantity and molecular weight. His dysferlin had a normal molecular weight, but his dysferlin concentration was only 50% of normal. Genetic analysis showed a heterozygous mutation in exon 55. Electromyography showed a myopathic pattern. A venous blood sample taken during fasting showed serum creatine phosphokinase, C-reactive protein, and fibrinogen values of 560 U/L (range 24–190), 3.5 mg/dL (range 0–1), and 555 mg/dL (range 200–400), respectively.

Spirometry was performed according to the American Thoracic Society recommendations. Respiratory muscle strength was assessed via multiple measurements of the maximum inspiratory pressure and maximum expiratory pressure at the mouth, generated against an occluded airway. P_{aO₂}, P_{aCO₂}, and pH were measured with the patient sitting and breathing room air for at least 30 min. Table 1 shows the pulmonary function test and blood gas results. Static lung volumes were determined via the helium-dilution method. His vital capacity was 2,240 mL (73% of predicted) in the sitting position, and decreased to 1,950 mL (64% of predicted) in the supine position. A nocturnal polysomnogram showed an apnea/hypopnea index of 26.2 episodes per hour (with apnea defined as absence of air flow for \geq 10 s, and hypopnea defined as a \geq 30% decrease in air flow associated with a \geq 4% decrease in S_{pO₂}).

To relieve airway obstruction, domiciliary inhaled bronchodilator was integrated with a 2-week course of oral prednisone (25 mg/d), after which we instituted nocturnal intermittent noninvasive ventilation (NIV) to prevent nocturnal hypoventilation and desaturations.

The prednisone substantially improved both spirometry and blood gases (see Table 1). Nocturnal oxyhemoglobin saturation was monitored with a pulse oximeter with a finger probe. On NIV his mean nocturnal S_{pO₂} increased from 91% to 95%, and the percent of sleep time with S_{pO₂} < 90% fell from 24% to 2%. After 2 weeks of nocturnal

NIV his blood gases further improved, to pH 7.42, P_{aCO_2} 45 mm Hg, and P_{aO_2} 86 mm Hg.

At a follow-up 2 years later he had satisfactory ventilation (see Table 1), his clinical condition was stable, he reported no further episodes of acute respiratory failure, and he no longer had exercise-induced dyspnea; exercise limitation was due mostly to limb weakness.

Discussion

Pulmonary involvement is frequent in neuromuscular diseases. The severity of pulmonary impairment and the disease stage at which it develops differ in the different types of neuromuscular disease.⁷

Stübgen et al reported that mild dyspnea on exertion, chronic cough, and recurrent respiratory-tract infections occur in patients with limb-girdle muscular dystrophies.⁷ In that study respiratory muscle weakness was common but mild, and the diaphragm was not disproportionately affected by the dystrophic process, compared to the limb muscles.⁷

In a study that included 60 patients with limb-girdle muscular dystrophies, there were only minimal changes in respiratory function and no evidence of respiratory hypoventilation, even in the patients who were not more ambulatory.⁸ In several other patients with limb girdle muscular dystrophies, mild pulmonary abnormalities were reported, but there were substantial blood-gas abnormalities in only 3 patients, who were already wheelchair-bound.² Differently from the above reports, our patient had severe diaphragm impairment, respiratory hypoventilation, and substantial blood-gas abnormalities while he was still ambulatory. To the best of our knowledge, among the limb-girdle muscular dystrophies, no respiratory dysfunction in dysferlinopathies have been reported.

Recently, clinical symptoms of skeletal muscle weakness were reported in 2 dysferlin-gene-mutation carriers,¹¹ but in those patients no respiratory muscle impairment was described.¹¹ Our patient had severe weakness of both skeletal (shoulder and pelvic girdles) and respiratory muscles, but no treatment, nutritional state, or electrolyte abnormalities explained that muscle impairment. Based on the timing of onset of his skeletal muscle impairment and COPD, it is tempting to hypothesize that systemic inflammatory response related to the COPD and the genetic dysferlin deficit interacted to create the respiratory and limb-girdle muscles weakness.

Patients with respiratory muscle weakness are at risk of respiratory failure during sleep, especially rapid-eye-movement sleep.¹² In patients with bilateral diaphragm paralysis the intercostals and accessory muscles become the principal muscles of inspiration. Inhibition of those muscles' activities during rapid-eye-movement sleep causes severe hypoventilation, apneas, and hypoxia.¹²

Later, nocturnal hypoxemia and hypercapnia may persist even during the daytime.

Our patient's arterial blood gases substantially improved after relieving the airway obstruction, but they normalized only after NIV treatment. In previous reports, satisfactory ventilation was maintained for more than 2 years, with NIV administered only during sleep.

Surprisingly, at a 2-year follow-up our patient's maximum inspiratory pressure had significantly increased above baseline, in contrast to what we would expect as a consequence of the unloading effect of NIV. A possible explanation is that the dysferlin deficit injures respiratory muscles, which are loaded by the airway obstruction, so NIV might have rested the fatigued respiratory muscles, which could have reduced their damage and weakness.

This case of respiratory muscle impairment in a patient with a dysferlinopathy underscores the importance of assessing pulmonary function both awake and asleep in patients affected by neuromuscular diseases. We suggest that COPD (possibly through its systemic inflammatory response) can influence the phenotypic expression of dysferlin deficiency.

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