Nemaline myopathy is a rare congenital myopathy that generally presents in childhood. We report a case of a 44-year-old man who presented with severe hypoxic hypercapnic respiratory failure as the initial manifestation of nemaline myopathy. After starting noninvasive ventilation, his pulmonary function test results improved substantially, and over the 4 years since diagnosis his respiratory function remained stable. There are few reported cases of respiratory failure in patients with adult-onset nemaline myopathy, and the insidious onset in this case is even more unusual. This case highlights the varied presenting features of adult-onset nemaline myopathy and that noninvasive ventilation improves respiratory function. Key words: nemaline myopathy, respiratory failure. [Respir Care 2008;53(11):1490–1494. © 2008 Daedalus Enterprises]

Introduction

Nemaline myopathy is a rare congenital myopathy that can have a varied presentation. Despite the congenital nature of nemaline myopathy, it may not present until adulthood. Its rarity and diverse symptoms can make it difficult to diagnosis. We saw a former athlete who presented with subacute respiratory insufficiency in middle age. Noninvasive ventilation (NIV) improved his symptoms and stabilized his respiratory function.

Case Report

A 44-year-old man was referred by his family doctor to the respiratory clinic for cough, dyspnea on climbing stairs, and reduced energy, for 8–12 weeks.

On detailed history, the patient stated that he had noted no weakness until 6 years ago, at age 38 years. Initially he had noted some mild lower-extremity weakness, which occasionally caused him to fall. He noted difficulty in moving his toes appropriately. He still walked approximately 1 km each morning but noted difficulty climbing hills or stairs, due to the weakness. This progressed to involve the upper limbs, and he had some difficulty abducting both arms and found it difficult to lift objects off a table. By the time of presentation to the respiratory clinic this had progressed to involve more proximal muscles, in particular the hip flexors. He had only noticed involvement of his shoulder girdle very recently.

The cough and shortness of breath were present prior to 4 months preceding respiratory review, and he had noted some problems with his breathing over the last 6 years. This had been characterized by a very insidious onset of dyspnea, about which he was slow to comment. He had not suffered respiratory infections. He did note morning headaches, daytime somnolence, and decreased concentration in the last year.

He was the son of healthy, non-consanguineous white parents. He had 6 siblings, 5 of whom were alive and well. One of his brothers was a smoker and had respiratory difficulties thought to be related to chronic obstructive pulmonary disease. There was no family history of neuromuscular disease. Our patient’s birth had been a full-term normal vaginal delivery and his mother did not note

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any respiratory or feeding difficulties in his neonatal period. His motor and speech development were normal and he had met the developmental milestones within expected norms. He described a normal childhood, in which he was able to run and play games without any limitations. He had played competitive football until his early thirties.

On initial examination he was noted to have cyanosis and chemosis. On respiratory examination he had poor chest expansion (only 3 cm), reduced air entry, crackles in the base of the left lung, reduced tidal percussion, and marked orthopnea. Cardiovascular examination was unremarkable.

Neurologic examination, including cranial nerve examination and fundoscopy, was normal. No facial weakness or fatigability was noted. There was bilateral muscle wasting at the superior head of the pectoralis major, the dorsal rotator cuff, and, to a lesser degree, the biceps and triceps. There was moderate and symmetrical weakness in: shoulder abduction and adduction; elbow flexion and extension; wrist flexion and extension; finger flexion, extension, and abduction/adduction; hip flexion, extension, and abduction/adduction; knee flexion and extension; ankle dorsiflexion; and plantar flexion and inversion/eversion. Coordination was normal throughout. Reflexes were present but reduced throughout. Proprioception, vibration, temperature, pain, and light touch were normal in the upper and lower limbs. Gait examination revealed a high-stepping gait with bilateral foot drop.

Blood tests showed polycythemia (hemoglobin 17.8 g/dL) but normal creatine kinase, aldolase, erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis, antinuclear antibody, rheumatoid factor, antineutrophilic cytoplasmic antibody, thyroid function, vitamin B12, and folate. Arterial blood gas analysis revealed hypoxic hypercapnic respiratory failure: pH 7.31, PaO2 80 mm Hg, PaCO2 40 mm Hg, and HCO3 39 mmol/L. Those values indicate severe hypoxia and hypercapnia. The elevated HCO3 indicates a compensatory metabolic alkalosis. However, that pH is low, which indicates only partial compensation and an element of acute-on-chronic respiratory failure.

Pulmonary function tests showed a classic restrictive pattern, with mainly extrathoracic involvement, consistent with neuromuscular problems (Fig. 1 and Table ).

Electromyogram showed spontaneous activity in most of the muscles tested, along with the predominantly short and low-amplitude motor action potentials, which suggest myopathy. He also had high-amplitude long action potentials, which is a mixed result that can sometimes be consistent with inflammatory myopathies. There was no neuromuscular evidence of a multifocal motor neuropathy or demyelinating process.

Left quadriceps and left triceps muscle biopsies (Fig. 2) showed multiple subsarcolemmal dark nemaline rods consistent with nemaline myopathy. Electron microscopy (Fig. 3) showed dense sarcoplasmic bodies originating from Z-bands.

Table 1. Pulmonary Function Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Value</th>
<th>Measured Value</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>4.65</td>
<td>1.53</td>
<td>33</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>3.80</td>
<td>1.28</td>
<td>34</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.79</td>
<td>0.84</td>
<td>106</td>
</tr>
<tr>
<td>FEF25-75 (L/s)</td>
<td>4.22</td>
<td>1.57</td>
<td>37</td>
</tr>
<tr>
<td>MEF (L/s)</td>
<td>9.06</td>
<td>4.72</td>
<td>52</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>6.98</td>
<td>3.20</td>
<td>46</td>
</tr>
<tr>
<td>RV (L)</td>
<td>2.04</td>
<td>1.65</td>
<td>81</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>0.31</td>
<td>0.52</td>
<td>167</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>3.42</td>
<td>2.01</td>
<td>59</td>
</tr>
<tr>
<td>MIP (cm H2O)</td>
<td>ND</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Sniff nasal inspiratory pressure (cm H2O)</td>
<td>ND</td>
<td>38</td>
<td>NA</td>
</tr>
<tr>
<td>Sniff nasal expiratory pressure (cm H2O)</td>
<td>ND</td>
<td>94</td>
<td>NA</td>
</tr>
</tbody>
</table>

FVC = forced vital capacity
FEV1 = forced expiratory volume in the first second
FEF25-75 = forced expiratory flow during the middle half of the forced vital capacity maneuver
MEF = maximum expiratory flow
TLC = total lung capacity
RV = residual volume
FRC = functional residual capacity
MIP = maximum inspiratory pressure
ND = no data available
NA = not applicable
We commenced NIV via oronasal mask, with a pressure-targeted mode, and titrated the settings based on overnight oximetry. He tolerated the NIV very well, and he stabilized at NIV inspiratory pressure of 10 cm H$_2$O and expiratory pressure of 4 cm H$_2$O. He was discharged and seen on an out-patient basis. During a later admission to review NIV settings, inspiratory pressure was titrated up to 16 cm H$_2$O and expiratory pressure to 6 cm H$_2$O. His pulmonary function test results continued to be consistent with a restrictive defect. His maximum inspiratory pressure at the time of diagnosis was 33 cm H$_2$O, and it was 31 cm H$_2$O at recent follow-up, 5 years after diagnosis. His maximum expiratory pressure has been in the range 86–100 cm H$_2$O (normal value for his age approximately 130 cm H$_2$O) over all the years of follow-up.

In the first few months after diagnosis he required supplemental oxygen. Following initial treatment with NIV plus oxygen for 3 months, oximetry indicated that supplemental oxygen was no longer required, and he has not used supplemental oxygen since then. His arterial blood gas values at 3 months were pH 7.41, P$_{CO_2}$ 40 mm Hg, P$_{O_2}$ 107 mm Hg, and HCO$_3$ 24.5 mmol/L while breathing room air. There was no longer evidence of carbon dioxide retention, and the acidosis had corrected. He no longer had orthopnea but always used NIV during sleep or any other extended period of lying down. The daytime somnolence, morning headache, and decreased concentration had resolved.

He performed the 10-m shuttle-walk test (an objective test of functional exercise capacity and index of disability for patients with chronic airflow limitation) within the first month of diagnosis, again after starting NIV, and again after 6 months of NIV. His 10-m shuttle-walk distance improved from level 7 (360 m) with a Borg breathlessness score of 7 (very severe) to level 8 (440 m) with a Borg breathlessness score of 3 (moderate). Originally he had desaturated to 85%, but on his follow-up tests he no longer desaturated, and the only limitation to his exercise was that his limb weakness made him unable to increase propulsion speed.

Recent physiotherapy evaluation found no change in muscle strength over the last 5 years, which indicates no further progression of the condition.

Discussion

Nemaline myopathy is a rare congenital myopathy that generally presents in childhood. In a series of 143 cases, presentation was typical congenital, severe congenital, intermediate congenital, childhood-onset, and adult-onset in 46%, 16%, 20%, 13%, and 4%, respectively.1 Weakness mostly affects the facial muscles, flexors of the neck and trunk, dorsiflexors of the feet, and extensors of the toes. The distal limb muscles and limb-girdle muscles are weaker than the proximal limb muscles. Sporadic late-onset nemaline myopathy is uncommon.

In making the diagnosis of nemaline myopathy, clinical suspicion is the first step. Creatine kinase may be normal or slightly elevated. Electromyography may show myopathic changes such as action potentials of small amplitude and short duration,2 but those changes are not spe-
cific. Diagnosis is confirmed with muscle biopsy, which shows characteristic rod bodies, best seen with modified Gomori trichrome staining.

The initial differential diagnosis in our patient included many causes of neuromuscular respiratory failure, including demyelinating neuropathy, an unusual myopathy, or mitochondrial disease. Motor neuron disease was considered, but the absence of wasting and symmetry was against that diagnosis. Myasthenia gravis was also considered, but there were no bulbar symptoms. Muscle biopsy provided the definitive diagnosis of nemaline myopathy.

Nemaline myopathy derives its name from the characteristic rod bodies in muscle, which appear threadlike in longitudinal section. Engel first described sporadic late-onset nemaline myopathy in 1966, in 2 patients. Since then much has been discovered about nemaline myopathy and its complex genetics.

Nemaline myopathy is clinically and genetically heterogeneous. Mutations in 5 different genes that code for sarcomeric proteins have been reported to cause nemaline myopathy: the nebulin gene, α-tropomyosin gene, β-tropomysin gene, α-actin gene, and the gene that encodes slow skeletal muscle troponin T. The 70th International Workshop on Nemaline Myopathy in 1999 reached consensus on 5 categories of nemaline myopathy: severe congenital (which is the typical form); intermediate congenital; mild childhood-onset or juvenile-onset; adult-onset forms; and other forms. Although the adult-onset forms have the inclusion criterion that onset is as an adult, age of onset is clearly not always the same as age at presentation, thus careful history-taking and scrutinizing of clinical notes are necessary to determine age of onset in individual cases.

After a normal childhood and appropriately reaching developmental milestones, our patient developed muscle weakness in adult life, so his was adult-onset nemaline myopathy.

Nemaline myopathy with respiratory symptoms is very uncommon. In 2005, Chahin et al described observations and long-term follow-up in 14 patients with sporadic late-onset nemaline myopathy, examined at the Mayo Clinic between 1975 and 2003. A conclusion of that study was that sporadic late-onset nemaline myopathy presents with subacutely evolving weakness after age 40. The weakness was predominantly proximal in 11 patients, equally proximal and distal in 3 patients, and asymmetric in 4 patients. The weakness began in the arms in 6 patients, and in 8 patients the arms were more severely affected than the legs. One patient had head-drop and 2 patients also had substantial abdominal-muscle weakness. Six patients had dysphagia. Sensory examination was normal in all the patients. No patient in that study presented with respiratory complaints.

Falgà-Tirado et al reported on a 49-year-old woman who presented with respiratory insufficiency from nemaline myopathy. Another case report was of a patient with mild nemaline myopathy and sleep hypoventilation due to a mutation in the skeletal muscle α-actin gene. That 39-year-old woman had a previous diagnosis of nemaline myopathy when she developed life-threatening respiratory failure following a pneumonia. Kudou et al described 2 cases of congenital nemaline myopathy that presented with respiratory failure: one had muscle weakness since birth, and the other presented with slowly progressing respiratory failure.

Our 44-year-old male patient presented with minimal clinical symptoms but severe hypoxic hypercapnic respiratory failure as the initial manifestation of adult-onset nemaline myopathy. Presentation with respiratory failure is exceptionally rare in nemaline myopathy. Previous published cases often had either preexisting nemaline myopathy or known muscle weakness from birth. Two case reports have described adult-onset nemaline myopathy that presented with respiratory failure. Our patient’s respiratory function initially improved and then stabilized with nocturnal NIV and has remained stable for the 5 years since diagnosis.

The reason(s) for our patient’s improvement and stabilization is unclear. Long-term mechanical ventilation has an established role in the management of ventilatory failure due to neuromuscular disease, having gained credence during the polio myelitis epidemics in the middle of the last century. It was not until the early 1980s that NIV via mask was pioneered by Rideau et al in France, and subsequently by Bach et al in the United States. Large-cohort studies found that NIV can extend survival in patients with nonprogressive conditions, such that these individuals are likely to have a nearly normal life expectancy. The benefits of nighttime NIV are sustained during the day. Several possible mechanisms have been considered. Hill suggested that NIV may work by improving ventilatory mechanics, resting fatigue respiratory muscles and thereby improving strength and endurance, or enhancing ventilatory sensitivity to CO₂. Some of the initial improvement in our patient may have been due to reversal of atelectasis, which is likely to be present because of chronic hypoventilation. Reversing the microatelectasis probably accounts for the improved FVC.

After intermittent ventilation, Annane et al found: increased daytime PaO₂; decreased PaCO₂ and total bicarbonate; unchanged vital capacity, total lung capacity, maximum inspiratory or expiratory pressure, or alveolar-arterial oxygen difference; decreased apnea-hypopnea index and time spent with arterial oxygen saturation < 90%; increased sleep efficiency and mean arterial oxygen saturation; and significantly increased ventilatory response to CO₂. The reduction in PaCO₂ after NIV correlated solely with the increase in the slope of ventilatory response to the CO₂ curve (r = −0.68, P = .008). They concluded that
improvement of daytime hypoventilation with nocturnal NIV may be from an adaptation of the central chemoreceptors to the reduction of profound hypercapnia during sleep, or from better sleep quality. Further work found that patients who used NIV for > 4 h per night had significantly improved hypercapnic ventilatory response and $P_{aCO_2}$ after 3 months, whereas in patients who averaged < 4 h of NIV per night, chemosensitivity and arterial blood gas values returned to baseline at 3 months, after initial improvement at 5 days.25 A Cochrane review from Annane et al, however, concluded that, although the evidence is directionally consistent, more randomized controlled trials of long-term nocturnal NIV in neuromuscular disease are required.26

Our patient made a rare presentation of a very uncommon condition. The case highlights the broad differential diagnosis of dyspnea, the varied presentation of adult-onset nemaline myopathy, and the potential respiratory-function benefit of NIV.

REFERENCES