Early Onset of Sleep-Disordered Breathing in Two Children With SEPN1-Related Myopathies

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Abstract

Selenoprotein-related myopathy (SEPN1-RM) is a rare disease with a variable clinical presentation. The selenoprotein N1 gene (SEPN1) mutation causing this congenital muscular dystrophy was identified in 2001. Sleep-disordered breathing (SDB) may occur in young patients with SEPN1-RM who are still able to walk. We report the cases of two children with SEPN1-RM who presented with SDB at the ages of 7 and 12 years and for whom long-term nocturnal noninvasive ventilation yielded significant improvement. Based on literature review and our current cases, it seems that there is no obvious relationship between the time since SDB onset and outcome of pulmonary function tests or limb muscle weakness. We therefore suggest that SDB should be systematically screened for in patients with SEPN1-RM, at regular intervals using nocturnal polysomnography.

Citation:


Keywords: congenital muscular dystrophy, noninvasive ventilation, polysomnography, respiratory insufficiency, selenoprotein, selenoprotein N1-related myopathies, sleep apnea syndrome, sleep-disordered breathing

INTRODUCTION

Selenoprotein-related myopathy (SEPN1-RM) is a rare autosomal recessive disease caused by SEPN1 mutation leading to selenoprotein deficiency and subsequent muscle weakness. The main clinical symptoms are axial hypotonia and scoliosis occurring at an early age as well as respiratory deterioration requiring noninvasive ventilation (NIV). Skeletal impairments, especially scoliosis, usually continue to progress; conversely, limb muscle weakness might remain moderate so patients often retain their gait abilities.1,2

Available guidelines on diagnosis and management of neuromuscular diseases mainly focus on frequent myopathies such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA).1,2 In DMD, sleep-disordered breathing (SDB) occurs mostly in adolescents or young adults when patients begin losing their gait ability. However, there is no official guidance for management of rare myopathies such as SEPN1-RM.

This work reports daytime and nighttime respiratory monitoring in two young children with SEPN1-RM who were still able to walk. Based on literature review and our current cases, we suggest close sleep monitoring in children with SEPN1-RM.

REPORT OF CASES

Case 1

A 3-year-old boy was referred for mild axial hypotonia present since his first year of life, associated hyperlordosis and arthrochalasis. He walked at 12 months. SEPN1-RM was suspected at the age of 7 years based on a positive Gower sign, calf atrophy, limb-girdle dystrophy, rigid cervical spine, high-arched palate, and nasal speech. A homozygous mutation of the SEPN1 ([19+73 del]) gene was identified in the patient and found in both parents born in the same Eastern Europe village. At the time of referral, the patient presented with moderately decreased lung volume and a forced vital capacity (FVC) at 62% of predicted normal value (Figure 1). Morning headaches raised suspicion of nocturnal hypercapnia, although no snoring or apnea were reported. In his medical history we noted an adenotonsillectomy because of infectious complications 2 years prior and our ear, nose, and throat examination was normal. Polysomnography showed obstructive apneas and hypopneas (OAH), mainly during rapid eye movement (REM) sleep, and capnography found nocturnal hypventilation as transcutaneous carbon dioxide pressure, or tePCO2, was higher than 50 mmHg in 98% of total sleep time (Table 1). After initiation of NIV (spontaneous/timed (S/T) mode with bilevel pressure), sleep quality improved and the headaches disappeared. At the age of 11 years, the scoliosis worsened and FVC decreased to 42% of predicted normal value. Now at the age of 13, the patient had no further respiratory exacerbation.
Case 2

A 3-year-old girl was referred for mild axial hypotonia, frequent falls, and global arthrocalasis from the age of 1 year. SEPNI-RM was suspected at the age of 7 years based on a positive Gower sign, shoulder girdle weakness, limb-girdle dystrophy, axial and facial muscle weakness, rigid spine, high-arched palate and nasal speech. A compound heterozygote mutation of the SEPNI gene ([f-19+73 del] and [Met1Val;ATG > GTG]) was identified.

At the age of 9 years, her sleep was normal without morning headaches, no respiratory symptoms, and moderately decreased lung volume with FVC at 42% of normal predicted value (Figure 1). The patient underwent adenotonsillectomy due to infectious complications 1 year prior and her ear, nose, and throat examination was normal. She presented with an allergy to dust mites but remained asymptomatic on antihistamines. A mild nighttime snoring pattern was noted at the age of 9 years, but nocturnal pulse oximetry and morning blood gases were normal. The polysomnography at the age of 11 years was normal (Table 1). The following year, daytime fatigue, nocturnal enuresis, and attention disorder appeared. A second polysomnography when the patient was 12 years old showed OAH occurring mainly during REM sleep, associated with desaturation and presence of hypercapnia (tc pCO2 > 50 mmHg at 12% total sleep time) (Table 1).

These clinical symptoms along with the deterioration of polysomnographic indexes (the OAH index had increased nearly fourfold), more severe desaturation, and nighttime hypercapnia prompted us to initiate S/T mode with bilevel pressure NIV, accordingly to the European Respiratory Society statement. This led to the disappearance of daytime fatigue and nocturnal enuresis. When the patient was 17 years old, FVC remained unchanged without any further respiratory exacerbation.

DISCUSSION

We hereby report two pediatric cases of patients with SEPNI-RM and early-onset SDB requiring nocturnal NIV. Polysomnography was performed and analyzed based on American Academy of Sleep Medicine guidelines. Diagnosis and management of SDB were conducted according to pediatric criteria of the European Respiratory Society statement.

Selenoprotein deficiency results in muscle weakness, as the protein is known to be involved in calcium metabolism and decreased oxidation reactions. Moreover, it was shown that the gene was also expressed in the pulmonary parenchyma. In Sepn1-/- homozygous mice, selenoprotein deficiency induces abnormal alveolarization, decreased pulmonary elastance and increased pulmonary compliance. Thus, deterioration of respiratory functions in SEPNI-RM may be caused by both respiratory muscle weakness and dysfunction of abnormal pulmonary structures.

Only few data are available on patients with SEPNI-RM. In the study from Schara et al., all 11 patients had lung restriction and 4 of them had nocturnal hypoventilation requiring NIV. Scotto et al. observed decreased lung function in 97% of the 41 patients with SEPNI-RM. The nocturnal respiratory dys-function assessed via pulse oximetry was present in 86% of patients and appeared early on, at a mean age of 13.2 years. Interestingly, abnormal oximetry was found in two children as young as 2 and 4 years old. In all patients treated by NIV, respiratory functions remained stable. Our two additional cases confirm that SDB may occur early on, at a time when patients can still walk and only present with mild lung restriction. Polysomnography typically showed a pattern of sleep OAH, predominant in REM sleep, and capnography showed nocturnal hypercapnia. NIV allowed the stabilization of lung volumes. In the study from Schara et al., the four patients with SDB had scoliosis and the two patients without scoliosis did not present with SDB. However, SDB is generally unrelated to the degree of scoliosis regardless of its etiology and our cases do not support the hypothesis of a link between scoliosis and SDB in patients with SEPNI-RM.
In conclusion, our cases highlight the scarcity of SDB-suggestive clinical symptoms, and the absence of an obvious relationship between SDB onset and lung restriction or limb muscle weakness. Therefore, we suggest that SDB should systematically and frequently be screened in all patients with SEPN1-RM, using polysomnography. Moreover, limb-girdle dystrophy associated with early onset of SDB should help in the diagnosis of SEPN1-RM. Larger prospective studies would be relevant to better define age of SDB onset and ascertain nocturnal explorations schedule in SEPN1-RM.

**DISCLOSURE STATEMENT**

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