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

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In 2 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 SEPN1-RM patients who are still able to walk. We report here 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 upon literature review and our current cases, it seems that there is no obvious relationship between time since SDB onset and outcome of pulmonary function tests or limb muscle weakness. We therefore suggest that sleep-disordered breathing should systematically be screened for in patients with SEPN1-RM, at regular intervals using nocturnal polysomnography.

KEYWORDS

Selenoprotein, Selenoprotein N1-related myopathies, congenital muscular dystrophy, noninvasive ventilation, polysomnography, respiratory insufficiency, 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)[3,4]. In DMD, 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 upon literature review and our current cases, we suggest a 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 based on a positive Gower's sign, calf amyotrophy, 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, he presented with moderately decreased lung volume and a forced vital capacity (FVC) at 62 % of predicted

normal value (Figure). Morning headaches raised suspicion of nocturnal hypercapnia, although no snoring or apnea were reported. In his medical history we noted an adenotonsillectomy due to for infectious complications 2 years prior and our ENT examination was normal. Polysomnography showed obstructive apneas and hypopneas (OAH), mainly during rapid-eye movement (REM) sleep, and capnography found nocturnal hypoventilation as tc pCO_2 was higher than 50 mmHg in 98% of total sleep time (TST), (Table). After initiation of NIV (spontaneous/timed (S/T) mode with bi-level pressure), sleep quality improved and the headaches disappeared. At the age of 11, the scoliosis worsened and FVC decreased to 42% of predicted normal value. Now at the age of 13, he had no further respiratory exacerbation.

Case 2 A 3-year-old girl was referred for mild axial hypotonia, frequent falls and global arthrochalasis from the age of 1 year. SEPN1-RM was suspected at the age of 7 based on a positive Gower's 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 SEPN1 gene ([-19+73 del] and [Met1Val;ATG>GTG]) was identified.

At the age of 8, her sleep was normal without morning headaches, no respiratory symptoms, and moderately decreased lung volume with FVC at 42% of normal predicted value (Figure). She underwent adenotonsillectomy due to infectious complications 1 year prior and her ENT examination was normal. She presented with an allergy to dust mites but remained asymptomatic on antihistamine drugs. A mild nighttime snoring was noted at the age of 9, but nocturnal pulse oximetry and morning blood gases were normal (Table). The polysomnography at the age of 11 was normal. The following year, daytime fatigue, nocturnal enuresis and attention disorder appeared. A second polysomnography at the age

of 12, showed OAH occurring mainly during REM sleep, associated with desaturation and presence of hypercapnia (tc pCO_2 > 50 mmHg in 12 % of TST) (Table).

These clinical symptoms along with the deterioration of polysomnographic indexes (the OAH index had increased nearly 4 times), more severe desaturation and nighttime hypercapnia prompted us to initiate spontaneous/timed (S/T) mode with bi-level pressure NIV, accordingly to the European Respiratory Society statement[5]. This led to the disappearance of daytime fatigue and nocturnal enuresis. At the age of 17, FVC remained unchanged without any further respiratory exacerbation.

DISCUSSION

We hereby report 2 pediatric cases of patients with SEPN1-RM and early-onset SDB requiring nocturnal NIV. Polysomnography was performed and analyzed based on AASM guidelines[6]. Diagnosis and management of SDB were conducted according to pediatric criteria of the European Respiratory Society statement[5].

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 alveolization, decreased pulmonary elastance and increased pulmonary compliance .Thus, deterioration of respiratory functions in SEPN1-RM may be caused by both respiratory muscles weakness and dysfunction of abnormal pulmonary structures[7].

Only few data are available on patients with SEPN1-RM. In the study from Schara *et al.*, all 11 patients had lung restriction and 4 out of them had nocturnal hypoventilation requiring NIV[1]. Scoto *et al.* observed decreased lung functions in 97% of the 41 patients

with SEPN1-RM. The nocturnal respiratory dysfunction assessed via pulse oximetry was present in 86% of patients and appeared early on, at a mean age of 13.2 years. Interestingly, they found abnormal oximetry in two children as young as 2 and 4 years old. In all patients treated by NIV, respiratory functions remained stable[2]. 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 obstructive apneas and hypopneas, predominant in REM sleep, and capnography showed nocturnal hypercapnia. NIV allowed the stabilization of lung volumes. In the study from Schara *et al.,* the 4 patients with SDB had scoliosis and the 2 patients without scoliosis did not present with SDB[1]. However, SDB is generally unrelated to the degree of scoliosis regardless of its etiology[8] and our cases do not support the hypothesis of a link between scoliosis and SDB in SEPN1-RM patients.

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 sleep-disordered breathing 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 .

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Figure. Trends in pulmonary function tests.

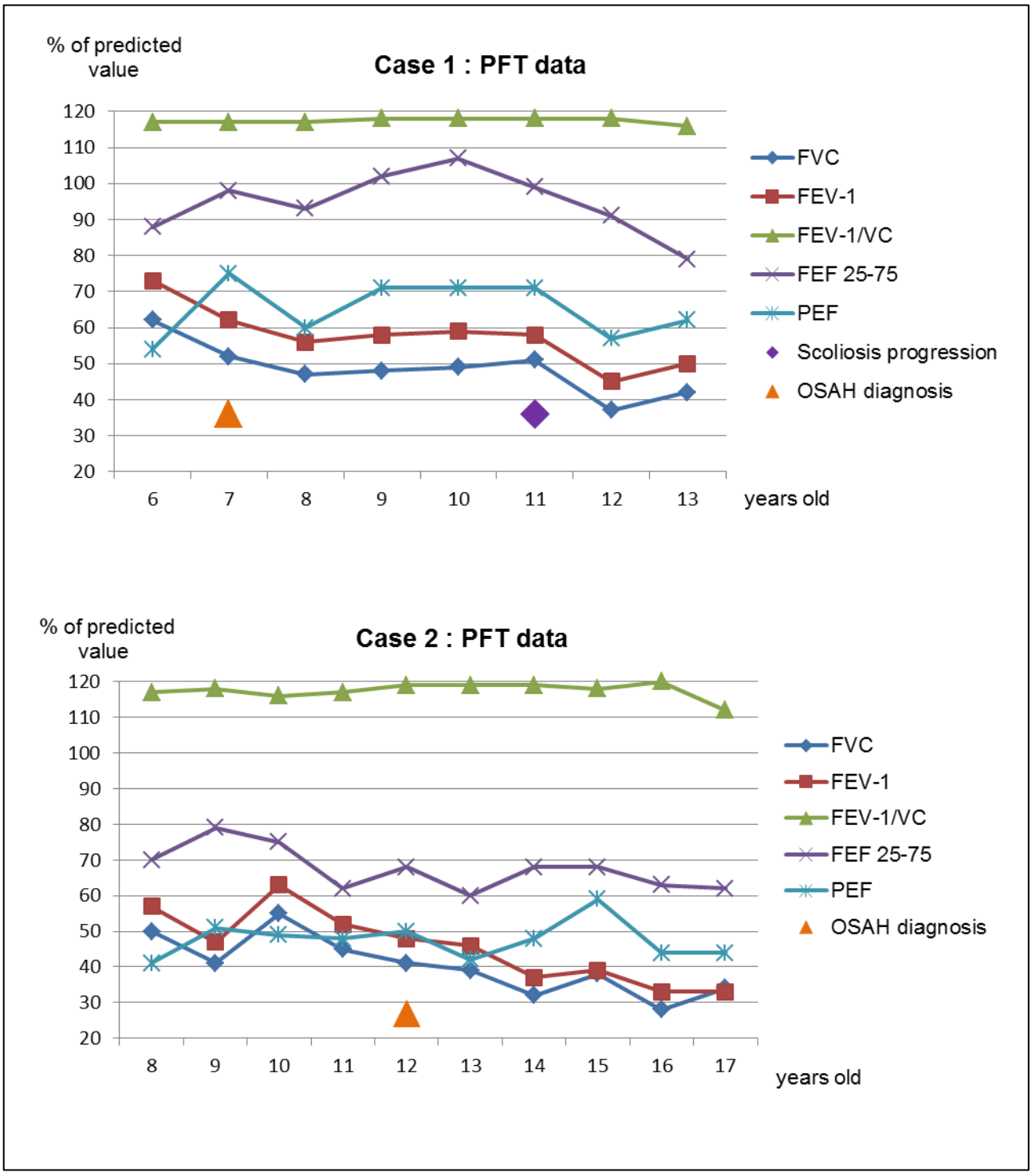

Table. Polysomnographic data.

	Case 1	**Case 2**	
Age	**8 y. o.**	**11 y. o.**	**12 y. o.**
Sleep analysis			
Total sleep time (TST), min	526	405	440
Sleep latency, min	43	37	25
Sleep efficiency, % of total time in bed	91	70	89
Sleep structure			
Stage 1, % of TST	8	18	3
Stage 2, % of TST	39	36	38
Stage 3, % of TST	35	26	26
Stage Rapid Eye Movement, % of TST	18	20	33
Respiratory events			
Apnea-hypopnea Index, n/h of TST (total number)	11 (97)	2.2 (15)	7.4 (54)
Obstructive apnea hypopnea Index, n/h of TST (total number)	6.8 (60)	0.4 (3)	3.1 (23)
Central apnea-hypopnea index, n/h of TST (total number)	4.2 (37)	1.8 (12)	4 (29)
Apnea Index, n/h of TST (total number)	0.1 (1)	0.1 (1)	0.7 (16)
Hypopnea Index, n/h of TST (total number)	10.9 (96)	2.1 (14)	6.6 (38)
Mean duration of apnea or hypopnea, sec	10	15	12
Maximal duration of apnea or hypopnea, sec	43	35	23
Non Rapid Eye Movement Sleep events proportion, %	33	73	17
Rapid Eye Movement Sleep events proportion, %	67	27	83
Pulse oxymetry			
Mean oxygen saturation, %	91	95	95
Minimal oxygen saturation, %	79	87	81
Desaturation index, n/h of TST	7	1	8
Nocturnal transcutaneous carbon dioxide pressure (tc pCO_2)			
Mean, mmHg	54	45	50
Maximal, mmHg	65	50	55
Sleep time with carbon dioxide pressure > 50 mmHg, % TST (min)	98 (511)	0 (0)	12 (64)
Sleep time with carbon dioxide pressure > 55 mmHg, % TST (min)	27 (145)	0 (0)	3 (16)
Daytime lung function			
Forced Vital Capacity (% of predicted normal value)	51	41	39