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## Highlights

- SEPN1-related myopathy is characterized by a predominant diaphragmatic dysfunction.
- This explains the high prevalence of sleep-disordered breathing.
- Weakness of the expiratory muscles is also observed in SEPN1-related myopathy.

- Noninvasive ventilation may stabilize the decline of respiratory muscle function.

**Abstract**

**Background** SEPN1-related myopathy (SEPN1-RM) is characterized by predominant axial muscle weakness, early scoliosis, rigid spine and severe respiratory insufficiency. The aim of the study was to characterize the mechanisms of respiratory dysfunction in SEPN1-RM patients.

**Methods** Breathing pattern and respiratory muscle strength were measured by means of esophageal (Pes) and gastric (Pgas) pressures.

**Results** Seven patients aged 7-55 years (1 adult) at first respiratory muscle test, were studied. Five patients were treated by nocturnal NIV≥4 months. Mean ΔPes was within normality during tidal breathing, but the ΔPgas/ΔPes index indicated an increased contribution of the rib cage and expiratory muscles, as compared to the diaphragm, in the pediatric patients and bilateral diaphragmatic paralysis in the adult patient. Forced vital capacity (FVC) was reduced in all patients (52±19%pr) with mean FVC seated-supine drop of 24±7%. Global inspiratory muscle and diaphragmatic strengths were moderately reduced in 2 patients, highly reduced in 4 patients and severely reduced in the adult patient. Expiratory muscle strength was moderately reduced in 6 patients and severely reduced in the adult patient. FVC and respiratory muscle strength remained stable in 2 patients treated by nocturnal NIV within a 3-year follow-up.

**Conclusion** Diaphragmatic dysfunction is a characteristic feature of SEPN1-RM and NIV may stabilize the decline in respiratory muscle strength.

**Key words:** SEPN1-related myopathy; rigid spine muscular dystrophy; noninvasive ventilation; diaphragm; respiratory function.

**Abbreviations:** SEPN1-related myopathy, Pes esophageal pressure, Pgas gastric pressure, FVC forced vital capacity, IPPB intermittent positive pressure breathing, MmD multiminicore disease, Pdi transdiaphragmatic pressure, ΔPgas Exp gastric pressure swing during expiration, PTPes esophageal pressure-time product, PTPdi diaphragmatic pressure-time products, FVCup Upright forced vital capacity, FVCsup supine forced vital capacity, SniffPes maximal sniff esophageal pressure, SniffPgas maximal sniff gastric pressure, SniffPdi sniff transdiaphragmatic pressure, Pgas cough gastric pressure during a maximal cough, TTdi diaphragmatic tension-time index, TTes esophageal tension-time index.

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## 1. Introduction

Selenoprotein N1, encoded by the *SEPN1* gene located on chromosome 1p36 (RSMD1 locus), is an endoplasmatic reticulum glycoprotein belonging to the selenoprotein family which contains selenium in the form of the amino acid selenocysteine and is expressed in numerous tissues, including skeletal muscle [1-3]. Although the precise function of SEPN1 protein is uncertain, recent studies suggest a role in redox-related calcium homeostasis and cell protection against oxidative stress [4]. Previous studies suggested a role for selenium in the physiopathology of striated muscles, showing an association between selenium deficiency and muscular dystrophy in livestock [5]. Myoblast and fibroblast obtained from patients with *SEPN1* mutations showed an increase in reactive oxygen species, suggesting a role for SEPN1 in maintaining the redox status of the muscle [3].

Mutations in *SEPN1* have been associated with the following autosomal recessive congenital myopathies: rigid spine muscular dystrophy, the classical form of multiminicore disease (MmD), desmin-related myopathy with Mallory body-like inclusions and, recently congenital fiber-type disproportion [6]. In spite of morphological differences, the clinical phenotype is homogeneous and patients share a very recognizable picture. This includes congenital or early onset generalized hypotonia, predominant axial muscle weakness with early rigid spine, and respiratory failure occurring in childhood or early adolescence [3]. The severity of respiratory impairment is however not correlated to limb skeletal muscle weakness and its evolution. Indeed, most of the time the proximal weakness remains stable into adulthood with acquired normal independent ambulation. In

contrast to limbs, which usually do not show marked weakness or joint contractures in childhood, axial involvement is usually present from early life with neck weakness and progressive spinal contractures leading to a very stiff spine [4]. Progressive deformity of the spine is often observed during childhood and further impairs respiratory function, due to a characteristic lateral translation and thoracic lordosis which can lead to tracheo-bronchial compression requiring surgical stabilization. This spinal stiffness is a useful clinical marker of the disease, as is the early respiratory failure which may cause life-threatening complications even in ambulant patients. Indeed, the major determinants of respiratory failure in SEPN1-related myopathy (SEPN1-RM) are poorly characterized. They are thought to be the weakness of accessory respiratory muscles (sternocleidomastoid, scalenes and intercostals muscles) [7], the stiffness of the rib cage and spine with increased thoracic penetration index [8] and, the presence of diaphragm dysfunction causing nocturnal hypoventilation requiring ventilatory support [1,5,9,10]. Therefore screening for nocturnal hypoventilation is crucial for management [6].

SEPN1 deficiency was also found to be associated with abnormal lung development in *Sepn1*$^{-/-}$ mice [2]. This was characterized by a robust increase in the size of the distal airspaces (alveolar enlargement) associated with increased rates of apoptosis of alveolar septal cells in the absence of lung inflammation. Respiratory mechanic assessment demonstrated higher lung compliance and lower lung elasticity in the *Sepn1*$^{-/-}$ mice, correlating well with the pathological findings. However, these findings need further investigation in human SEPN1-RM patients. Scoto *et al*. [4] reported a decline in forced vital capacity (FVC) already present in the first years of life. They found a negative correlation between predicted values of FVC and age and the increasing need for

nocturnal noninvasive ventilation (NIV) due to sleep-disordered breathing or respiratory failure [4]. Moreover Ferreiro *et al.* [9] observed a significant drop in supine FVC in patients with MmD, suggesting diaphragmatic involvement. However, the strength of the diaphragm and other respiratory muscles has never been reported in patients with these disorders. The aim of our study was therefore to characterize the respiratory muscle phenotype of children and adults harboring mutations in SEPN1.

## 2. Material and methods

### 2.1 Patients

The charts of all the patients with a genetically confirmed SEPN1-RM, followed at our multidisciplinary neuromuscular clinic, were retrospectively reviewed between 2007 and 2015. Molecular studies and clinical data were collected. Complementary data, including motor function and muscle biopsy findings, were gathered when available. The use of intermittent positive pressure breathing (IPPB) for hyperinsufflation therapy or assisted cough, NIV and, trunk orthotic treatments such as brace and plaster were reported.

NIV was initiated in case of diurnal hypercapnia (arterialized carbon dioxide tension >45 mmHg), nocturnal hypercapnia (transcutaneous carbon dioxide >50 mmHg for at least 2% of night time) and/or a minimal pulse oximetry <90% for at least 2% of night time [11,12].

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.

## 2.2 Procedures

### 2.2.1 *SEPN1* sequencing or molecular studies

Genomic DNA was extracted from blood samples using standard procedures after informed consent according to the local ethics committees. The 13 exons of *SEPN1* and the 3'UTR SECIS element were sequenced by Sanger sequencing using specific primers located in adjacent intronic regions. Exon 1 required the GC-rich PCR system kit (Roche). Sequences were analyzed with the Seqscape Software (Life Technologies).

### 2.2.2 Lung function and respiratory muscle tests

Lung function and respiratory muscle tests were recorded during stable clinical conditions in the upright position, as per ATS/ERS standards [13,14].

*Non volitional tests*

Respiratory rate ($f_R$) and tidal volume per weight ($V_{T/KG}$) were measured and, the rapid shallow breathing index ($f_R/V_T$) was calculated [15]. Subsequently, an oesogastric catheter (Gaeltec, Dunvegan, Isle of Skye, UK) was inserted pernasally after local anesthesia (lidocaine 2%, AstraZeneca, Rueil-Malmaison, France). Appropriate placement of the catheter was checked [16]. Transdiaphragmatic pressure (Pdi) was obtained by subtracting online the esophageal pressure (Pes) signal from the gastric pressure (Pgas) signal. All the following measurements were done on 10 steady respiratory cycles and mean values were determined. The Pes ($\Delta$Pes), Pgas ($\Delta$Pgas) and Pdi ($\Delta$Pdi) swings were measured. The Pgas swing during expiration ($\Delta$Pgas Exp) was also measured to assess expiratory muscles activity. $\Delta$Pgas Exp was calculated on the

Pgas trace as the difference between the maximal end-expiratory level to the minimal value reached during the following inspiration (Figure 1A) [17]. The presence of a positive ΔPgas Exp was considered as abnormal [18].

The ratio of the tidal swing in Pgas to swing in Pes (ΔPgas/ΔPes) was calculated to assess the relative contribution of the respiratory muscles to tidal breathing [19]. In healthy subjects, the ratio is equal to or more negative than -1. A value ranging between -1 and 1 indicates an ever-increasing contribution of the rib cage and expiratory muscles to tidal breathing, as compared with the diaphragm. With complete bilateral diaphragmatic paralysis, the ratio is equal or superior than 1.

The patient's inspiratory effort was assessed during spontaneous breathing by calculating the esophageal (PTPes) and diaphragmatic pressure-time products (PTPdi) [20]. Both PTPes and PTPdi were then expressed per minute (PTPes/min and PTPdi/min).

*Volitional tests*

Upright FVC (FVC*up*) (*Morgan Spiroflow* spirometer, PK Morgan Ltd, UK) was measured and, supine FVC (FVC*sup*) was reported when available.

In order to determine the strength of the inspiratory muscles, maximal sniff Pes (SniffPes), Pgas (SniffPgas), and Pdi (SniffPdi) were recorded. Gastric pressure during a maximal cough (Pgas cough) was measured to assess the strength of the expiratory muscles.

Fatigue of the diaphragm and the global inspiratory muscles was assessed by measuring diaphragmatic tension-time index (TTdi) and esophageal tension-time index (TTes), respectively [14,21].

## 3. Results

### 3.1 Clinical findings

The data of seven patients (5 females) were analyzed (Table 1). All patients harbored two mutations in the *SEPN1* gene. Muscle biopsy presented with different patterns in the 6 patients in whom it was performed (Table 1). Age at first visit for the respiratory muscle study ranged between 7 and 55 years old, with only one adult (#7). All the patients showed very low body mass index (<-2 SD) and short height.

Clinically, all patients had onset during early childhood with hypotonia and neck or axial and proximal weakness, but they all walked independently, at a normal (#2, #5, #6 and #7) or late age (#3, #4). Most patients were never able to run and always experienced difficulties climbing stairs and walking long distances, with a certain degree of proximal muscle fatigue. All were still able to walk at the time of the tests. No major limb joint contractures were noted. Motor function measure (MFM) was performed in two patients and showed a relatively conserved motor function (total score >70%).

Spinal stiffness and rigid spine were always noted in the first decade of life, and were associated with scoliosis in four patients before puberty (#1, #4, #6, #7). A thoracic scan showed an increased spinal penetration index in five cases (#3, #4, #5, #6, #7). Several patients wore braces, but patient #7 did not tolerate it initially and developed a subacute respiratory failure at the age of 11 years, which progressed to hypercapnic coma, revealing the respiratory dysfunction. A rigid plexidur brace (Garches type) was then used and well tolerated until the patient had spinal surgery at 16 years old [22].

All patients showed restrictive respiratory insufficiency of variable severity and, six patients (all except #2) required nocturnal NIV, which was initiated because of clinical signs of nocturnal hypoventilation, independently of absolute values of FVC (Table 1). NIV was started between 4 months to 44 years prior to the respiratory muscles testing in patients #1, #3, #5, #6 and #7. Only patient #4 started NIV after the respiratory muscles testing and consecutive abnormal sleep study. No patient required invasive ventilation by tracheotomy.

### 3.2 Lung function and respiratory muscle data at first assessment

$f_R/V_T$ was increased (167±63 breaths/min/L) during spontaneous breathing, indicating a rapid and shallow breathing (Table 2). Abdominal expiratory activity was observed in all the patients, except in patient #7, with a mean ΔPgas Exp of 6±2 $cmH_2O$ (Figure 1A). By contrast, both ΔPgas and ΔPdi were in phase with ΔPes in patient #7 (Figure 1B). ΔPgas/ΔPes ranged between -0·35 and -0·07, in patients #1 to #6, while in patient #7, ΔPgas/ΔPes was 2·95, indicating bilateral diaphragmatic paralysis (Table 3). PTPes/min was normal in all the patients, ranging between 86 and 135 $cmH_2O$.s/min, while PTPdi/min varied largely among patients (range 11-137 $cmH_2O$.s/min), showing abnormally low values in patients #1, #3, #4, and #6. In patient #7, PTPdi was not calculated due to the negative ΔPdi swing.

Mean FVC*up* was reduced (52±19%pr), indicating a restrictive pattern, with wide variations among patients (Table 3). Simultaneous FVC*up* and FVC*sup* measurements were available in all the patients except patients #1 and #7. The mean FVC*up-sup* drop was 24±7% (range 2-34%), with only patient #4 having a value over 25% (Table 3).

SniffPes and SniffPdi values were reduced in patients #2 and #4 (mean SniffPes, -52±9 $cmH_2O$; mean SniffPdi, 40±0 $cmH_2O$), highly reduced in patients #1, #3, #5, and #6 (mean SniffPes, -30±4 $cmH_2O$; mean SniffPdi, 18±7 $cmH_2O$), and severely reduced in the adult patient #7 (Table 3). SniffPgas values were negative in all the patients, except patients #2 and #5, suggesting diaphragmatic dysfunction. In patients #2 and #5, a short initial positive deflection was still present, suggesting an onset of diaphragm contraction with a secondary failure (Table 3, Figure 2). In patient #7, SniffPgas and SniffPdi harbored a particular flat shape in parallel with a plateau in SniffPes (Figure 1D), as compared to the pattern observed in the other patients (Figure 1C). PgasCough was reduced in all patients, ranging from 23 to 77 $cmH_2O$, with comparable values among patients, except patient #7 who had a severe weakness (Table 3).

TTes values were normal in all the patients ranging from 0·03 to 0·13, while TTdi values were normal in the 3 patients (#2, #3, #5) in whom it was calculated (range 0·03-0·07) (Table 2). In the others patients, TTdi was not calculated because of a particular "V" shape on ΔPdi due to the presence of expiratory muscle activity, leading to negative values. Indeed, Pdi first sharply decreases at the beginning of inspiration and then increases, instead of continuously increasing through inspiration as in normal subject, due to positive ΔPgas Exp.

### 3.3 Follow-up measurements

Two patients (#1 and #3) had 2 consecutive respiratory muscles testing within a 3-year follow-up period: at 16 and 31 months after the first evaluation in patient #3 and, at 4 and 31 months in patient #1. Both patients were treated by nocturnal NIV for 4 and 5 months

respectively before the first respiratory muscle tests. In patient #3, an important reduction of the FVC*up-sup* drop was observed. A decrease in $f_R/V_T$ and ΔPgas Exp was also observed over time in the 2 patients. PTPes/min and PTPdi/min remained stable over time in patient #1. In patient #3, they remained constant between 9 and 10 years old with a sharp reduction at 11 years old, even though PTPes/min was still within normal. Respiratory muscle strength remained quite stable during the 3 years follow-up in both patients.

## 4. Discussion

This study confirms that SEPN1-RM is characterized by an early and predominant diaphragmatic dysfunction, explaining the high rate of sleep-disordered breathing and need for NIV in these patients. To our knowledge, this is the first study to use oesogastric pressure measurements to ascertain diaphragmatic dysfunction. Other main findings were the presence of expiratory muscle activity during spontaneous breathing, and a weakness of expiratory muscles in all patients. The adult patient presented bilateral diaphragmatic paralysis.

### 4.1 Tidal mechanics

The recording of Pes and Pgas during spontaneous breathing was very informative. The ΔPgas/ΔPes ratio was quite similar in the pediatric patients (aged 7-18 years old), indicating a proportionally greater activity of the intercostal-accessory muscles, while it suggested a bilateral diaphragmatic paralysis in the adult patient (#7). The presence of expiratory muscle activity is an alternative adaptive mechanism to compensate for

diaphragmatic weakness. Indeed, contraction of abdominal muscles during expiration displaces the abdomen inward and the diaphragm cephalad. Relaxation of the abdominal muscles at the onset of subsequent inspiration causes outward abdominal motion and passive descent of the diaphragm [19,23]. This phenomenon occurred in all the patients with diaphragmatic dysfunction, and was probably present in patient #7. Indeed, patient #7 also presented a negative ΔPdi, which could be explained by the relaxation of passive diaphragmatic tension induced in expiration by abdominal muscle activity. In patient #7, the rise in Pgas due to expiratory muscle recruitment in the preceding expiration may be incompletely transmitted to the thorax because of the generation of passive diaphragmatic tension. This may generate a more negative ΔPgas than ΔPes, and therefore a negative ΔPdi. This explanation, however, has not been proven [19].

### 4.2 Vital capacity

Positional vital capacity is another approach to detect diaphragmatic weakness [24]. We found the highest FVC*up-sup* drop in patient #4 (34%). Patients #2, #3 and #6 had values close to the threshold value indicating diaphragmatic weakness (25%) [24]. In patient #7, the FVC*up-sup* drop could not be assessed, because the patient was not able to lay supine. These findings are in concordance with the data of Ferreiro *et al.* [9] who found FVC drop values between 14-46%. In patient #4, NIV was therefore indicated following the respiratory muscle assessments, because of associated sleep-disordered breathing.

FVC*up* %pr evidenced a restrictive respiratory pattern as observed in other studies [1,6,9], with a large range among patients and only patients #1 and #7 harboring a severe reduction. In the patients with a low FVC*up* %pr, one could probably exclude a weakness

of intercostal/accessory and abdominal muscles at the time of the first assessment. Indeed, ΔPes and PTPes/min were within normality and abdominal expiratory activity was present in all the patients.

### 4.3 Respiratory muscle strength

Concerning inspiratory muscle strength, different patterns could be evidenced. Patients #2 and #4 presented the lowest reduction in strength as compared with the other patients. Patient #7 was the most severely affected. SniffPgas values were negative in all the patients, except 2 patients, suggesting diaphragmatic dysfunction. In patients #2 and #5, SniffPgas was still positive but severely reduced, indicating that at the time of the study, the diaphragmatic dysfunction was of lower extent as compared to the other patients. The SniffPes, SniffPgas and SniffPdi shapes observed in patient #7 are of particular interest. The pressure plateaus correspond to a slowing of the inspiratory muscle relaxation rate (the analogy of skeletal muscle relaxation rate for respiratory muscles) [25]. Interestingly, sniff tests were the second tests performed by patient #7. This may exclude fatigability due to the numerous tests performed on the day of the respiratory muscle assessments. However this may underline the fact that performing such tests may be equivalent to an exhaustive exercise.

Expiratory muscle weakness was observed at a young age but remained quite stable until adolescence. However, more data are needed to understand the evolution of expiratory muscle weakness in these patients.

### 4.4 Respiratory management

The patients had different respiratory managements at the time of the respiratory muscle assessment with only patients #1, #3, #5, #6 and #7 being treated with daily IPPB and nocturnal NIV. Only the inspiratory muscle strength appeared to be lower in these patients when compared to the 2 patients who did not required NIV (one of them required NIV 6 months later). The lack of differences in the breathing pattern may be explained by the presence of compensatory mechanisms to guarantee correct ventilation, such as the use of accessory respiratory muscles or increase in neural respiratory drive. In patients #1 and #3 who repeated the respiratory muscle tests, FVC and respiratory muscle strength remained quite stable over time, suggesting that NIV and IPPB could slow down the decline of respiratory muscle strength. FVC*up-sup* drop highly improved in patient #3, while diaphragmatic strength in the seated position remained quite stable, suggesting that NIV could have a greater effect on diaphragm function in the supine position [10]. The fall in volume in the supine position may be the result of abdominal contents being moved into the chest, decreased effectiveness of the intercostal muscles (which are relatively shortened by the expanded rib cage), and an increase in chest wall elastance (caused by rib cage expansion). However, in order to understand the pathophysiological benefits of NIV, more data are required. A lower FVC*up-sup* drop was also reported in patients #4, #5 and #6 after NIV initiation (FVC*up-sup* drop before NIV >25% in patients #5 and #6, FVC*up-sup* drop <25% in patient #4 after NIV; data not shown). Scoto *et al.* [4] observed no clear progressive deterioration of the respiratory function after initiation of nocturnal NIV and, concluded that nocturnal NIV was very effective. Concerning the reduction in $f_R/V_T$ and ΔPgas Exp over time, this could be due either to a beneficial effect of nocturnal NIV on daily spontaneous ventilation or a worsening of the disease, leading

to a progressive weakness of the accessory inspiratory muscles. The latter could eventually explain the sharp reduction of PTP/min in patient #4. This point warrants further longitudinal data. Of note, adherence to NIV was difficult, with some patients having difficulties to accept and use nocturnal NIV on a daily basis. Further studies should also assess longitudinal respiratory evolution according to NIV adherence and age at which NIV is initiated. Indeed, we believe that a regular use of nocturnal NIV and IPPB may enhance the respiratory muscles unloading, increase the compliance of the respiratory system, and therefore limit the deterioration of the respiratory function. As such, a systematic evaluation of FVC*up-sup* drop should be proposed, on a yearly basis, by the age of 5 years old when the child is able to understand and perform the maneuver. This should be associated with the breathing pattern and respiratory muscle testing assessed using the oesogastric catheter and a systematic sleep study. NIV should be proposed in patients with a FVC*up-sup* drop over 25% coupled with reduced respiratory muscle strength and diaphragmatic dysfunction, even prior to abnormal sleep study.

### 4.5 Limitations of the study

Our study has several limitations. First, the number of patients is small, however SEPN1-RM are less common than other neuromuscular diseases. Second, longitudinal follow-up was not available for all the patients. Indeed such information is essential to understand the long-term course of respiratory muscles in SEPN1-RM and assess the potential benefits of the different respiratory therapies such as IPPB and NIV [26,27]. Moreover, we compared data of patients who were treated with IPPB and NIV during variable time periods prior to the respiratory muscle assessment with patients not treated with IPPB

and/or NIV. Third, rib cage and abdominal motions were not measured simultaneously to assess the presence of expiratory muscle activity in the patient with bilateral diaphragmatic paralysis. Finally, nocturnal poly(somno)graphy was not available in all the patients. This important point should be considered in future studies, knowing the major risk of nocturnal hypoventilation in patients with diaphragmatic dysfunction [28,29].

## 5. Conclusion

This study confirms the specific diaphragmatic dysfunction in patients with SEPN1-RM and, suggests a potential efficacy of NIV to slow down respiratory muscle decline, the main determinant of vital prognosis in this condition.

## 6. Conflicts of interest: none.

## 7. References

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**Figure 1. Breathing pattern and sniff test tracings of patient #6 (A and C) and patient #7 (B and D).**
Note the presence of an important ΔPgas Exp (arrow) as compared to inspiratory ΔPgas (bold arrow) in patient #6 (A), leading the particular "V" shape observed on ΔPdi. Indeed, Pdi first sharply decreases at the beginning of inspiration and then increases, instead of continuously increasing through inspiration as in normal subject. In patient #7 (B), Pgas and Pdi swings are in phase with Pes as observed in case of diaphragmatic paralysis.
Sniff measures were low in the patient #6 (C) and very low with patient #7 (D). Moreover SniffPgas was negative in both patients, indicating a diaphragmatic dysfunction during a volitional maneuver. Of note the negative SniffPdi and the particular shape of SniffPes, SniffPgas and SniffPdi in patient #7, with the occurrence of pressure plateaus, reflecting a slowing in inspiratory muscle relaxation rate. The pressure plateau was observed following the sniff effort on the Pnas and Pes tracings, while it was present during the whole effort on Pgas (and Pdi).
Pes: esophageal pressure; Pgas: gastric pressure; ΔPgas Exp: gastric pressure swing during expiration; Pnas: nasal pressure; Pdi: transdiaphragmatic pressure; I: inspiration; E: expiration; SniffPes: esophageal pressure during a sniff; SniffPgas: gastric pressure during a sniff; SniffPdi: transdiaphragmatic pressure during a sniff.

**Figure 2. Individual data of inspiratory muscle strength (sniff test).**
A: Evolution of esophageal pressure during a sniff maneuver (SniffPes); B: Evolution of gastric pressure during a sniff maneuver (SniffPgas); C: Evolution of transdiaphragmatic pressure during a sniff maneuver (SniffPdi).

**Table 1. Clinical and genetic data of the patients at the time of the respiratory muscle tests.**

| Patient (Sex) | Age Origin | Weight/Height Z-score BMI/Height | Family history | Mutation Inheritance | Muscle Biopsy | Walking acquisition | Maximal motor function | Current motor function | Spine defect/ Treatment | Criteria for NIV | Respiratory Treatments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 (F) | 7 yr Indian | 18kg/120cm -2·8/-0·3 | No | p.Cys277_462delins187 (c.827_829 dup[CCT]) Homozygous | NA | NA | Walk | Able to walk but fatigability | RSS, scoliosis Brace | Abnormal sleep study | NIV since 4 mo before the exam |
| 2 (M) | 8 yr Caucasian | 19kg/126cm -3·7/-0·4 | No | Substitution p.Met1Leu (c.1A>T) + duplication 10 nucl →early stop codon c.3_12dup | Mildly myopathic | 14 mo | Walk | Able to walk but fatigability | RSS | -- | No |
| 3 (F) | 9 yr Maghrebian | 18kg/121cm -3·4/-2·0 | No | Duplication 8 nucleotides in exon 1: c.66_73dup (p.Arg26Hisfsx43) Homozygous | Mildly dystrophic | 22 mo | 11 yrs | Able to walk but fatigability MFM (TS): 93% | RSS, thoracic lordosis | Diurnal hypercapnia + Abnormal sleep study | NIV since 5 mo before exam + IPPB |
| 4 (F) | 10 yr Pakistan | 28kg/128cm -2·6/-1·6 | 2 siblings | exon 8 c.1092+1G>A Homozygous | Multiminicore | 24 mo | Walk | Able to walk but fatigability | RSS, scoliosis Brace | Abnormal sleep study | No (NIV started 6 mo after exam) |
| 5 (M) | 12 yr Caucasian | 16kg/127cm -5·3/-3·1 | 1 sister | Duplication in exon 5 c.713dup + Substitution false sense in exon 11 p.Arg466Gln | Mildly dystrophic | 17 mo | Running | Able to walk but fatigability MFM (TS): 78% | RSS, thoracic lordosis | Diurnal hypercapnia + Abnormal sleep study | NIV since 1 yr before exam + IPPB |
| 6 (F) | 18 yr Caucasian | 31kg/149cm -2·3/-2·2 | No | p.Met1Arg Htz (c.2T>G) + p.Glu356X Htz (c.1066G>T) | Mildly myopathic | 12 mo | Walk | Able to walk but fatigability | RSS, L-scoliosis Brace | Diurnal hypercapnia + Abnormal sleep study | NIV since 3 yrs before exam + IPPB |
| 7 (F) | 55 yr Maghrebian | 33kg/154cm 13·9* | 2 siblings dead at 13 and 19 yrs for respiratory failure | Duplication 22 nucleotides10pb in exon 1, Frameshift Homozygous | Dystrophic | 13 mo | Walk | Able to walk at home but fatigability Wheelchair outdoor | RSS, L-scoliosis Brace Spinal fusion 16 yr | Hypercapnia coma | NIV since 44 yrs before exam |

Abbreviations: BMI: body mass index; IPPB: intermittent positive pressure breathing; L-scoliosis: lordosis and scoliosis; NIV: noninvasive ventilation; RSS: rigid spine syndrome; NA: not available; MFM (TS): Motor Function Measure (total score).
*BMI.

**Table 2. Breathing pattern and respiratory output.**

| Patient (Sex) | Age at muscle test (yrs) | Spontaneous breathing | | | | | | | | | Volitional maneuver | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FR (b/min) | VT/kg (ml/kg) | FR/VT (b/min/L) | ΔPes ($cmH_2O$) | ΔPgas ($cmH_2O$) | ΔPgas Exp ($cmH_2O$) | ΔPdi ($cmH_2O$) | PTPes/min ($cmH_2O$.s/min) | PTPdi/min ($cmH_2O$.s/min) | TTes | TTdi |
| 1 (F) | 7 | 42 | 7·9 | 295 | -9·9 ± 1·8 | 1·2 ± 0·5 | 7·8 ± 1·2 | 7·1 ± 0·6 | 97 | 14 | 0·08 | |
| | 8 | 33 | 7·8 | 220 | -6·9 ± 0·3 | 0·8 ± 0·6 | 7·9 ± 0·9 | 4·0 ± 0·8 | 107 | 13 | 0·07 | |
| | 10 | 34 | 6·4 | 189 | -6·9 ± 0·8 | 0·5 ± 0·3 | 3·2 ± 0·5 | 4·5 ± 0·4 | 93 | 13 | 0·08 | |
| 2 (M) | 8 | 35 | 10·6 | 175 | -8·9 ± 1·5 | 2·4 ± 0·7 | 3·1 ± 0·7 | 8·4 ± 1·8 | 133 | 137 | 0·06 | 0·07 |
| 3 (F) | 9 | 27 | 11·1 | 135 | -9·2 ± 1·8 | 2·1 ± 0·5 | 6·9 ± 1·2 | 4·6 ± 1·2 | 135 | 35 | 0·07 | 0·03 |
| | 10 | 22 | 12·6 | 91 | -9·3 ± 1·7 | 2·7 ± 0·7 | 5·5 ± 0·8 | 6·9 ± 1·6 | 135 | 51 | 0·08 | 0·05 |
| | 11 | 20 | 8·9 | 112 | -5·4 ± 1·0 | 1·0 ± 0·2 | 3·9 ± 0·51 | 3·7 ± 1·0 | 62 | 12 | 0·03 | |
| 4 (F) | 10 | 30 | 7·5 | 143 | -9·0 ± 1·0 | 1·7 ± 0·4 | 6·3 ± 1·2 | 5·3 ± 0·6 | 114 | 12 | 0·03 | |
| 5 (M) | 12 | 26 | 13·1 | 124 | -7·2 ± 0·4 | 2·5 ± 0·5 | 4·1 ± 1·0 | 6·4 ± 1·0 | 133 | 91 | 0·07 | 0·05 |
| 6 (F) | 18 | 44 | 7·6 | 187 | -6·1 ± 1·0 | 1·5 ± 0·7 | 6·6 ± 0·6 | 3·0 ± 1·3 | 110 | 11 | 0·05 | |
| 7 (F) | 55 | 24 | 6·7 | 109 | -4·2 ± 0·4 | -12·4 ± 0·6 | | -9·1 ± 0·7 | 86 | | 0·13 | |

Abbreviations: $f_R$: Respiratory rate; $V_T$: tidal volume; $V_{T/KG}$: tidal volume per kilogram; $f_R/V_T$: rapid shallow breathing index; ΔPes: esophageal pressure swing; ΔPgas: gastric pressure swing; ΔPgas Exp: Pgas swing during expiration; ΔPdi: transdiaphragmatic pressure swing; PTPes/min: esophageal pressure-time support per minute; PTPdi/min: diaphragmatic pressure-time products per minute; TTes: esophageal tension-time index; TTdi: diaphragmatic tension-time index.

**Table 3. Lung function and variations of esophageal (Pes), gastric (Pgas) and transdiaphragmatic pressure (Pdi) during spontaneous breathing and volitional maneuvers.**

| Patient | Age at exam (yrs) | FVCup/sup (%pr) | Drop FVCup/sup (%) | Spontaneous breathing | Volitional maneuver | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | ΔPgas/ΔPes | SniffPes ($cmH_2O$) | SniffPgas ($cmH_2O$) | SniffPdi ($cmH_2O$) | PgasCough ($cmH_2O$) |
| 1 | 7 | 19 / NA | NA | -0·12 | -25 | -15 | 10 | 57 |
| | 8 | 27 / NA | NA | -0·12 | -29 | -18 | 12 | 72 |
| | 10 | 27 / NA | NA | -0·07 | -22 | -14 | 11 | 46 |
| 2 | 8 | 71 / 55 | 23% | -0·27 | -45 | 4 | 40 | 67 |
| 3 | 9 | 69 / 53 | 23% | -0·23 | -32 | -15 | 17 | 77 |
| | 10 | 51 / 48 | 6% | -0·29 | -32 | -14 | 20 | 79 |
| | 11 | 55 / 47 | 14% | -0·19 | -33 | -10 | 23 | 75 |
| 4 | 10 | 47 / 31 | 34% | -0·19 | -58 | -21 | 41 | 72 |
| 5 | 12 | 56 / 55 | 2% | -0·35 | -30 | 2 | 26 | 57 |
| 6 | 18 | 48 / 40 | 17% | -0·25 | -33 | -15 | 20 | 65 |
| 7 | 55 | 15 / NA | NA | 2·95 | -11 | -15 | -7 | 23 |

Abbreviations: Drop FVCup-sup: percentage of variation between upright and supine forced vital capacity; FVC*up*: upright forced vital capacity; FVC*sup*: supine forced vital capacity; ΔPgas/ΔPes: ratio of the tidal swing in Pgas to the tidal swing in Pes; SniffPes: sniff esophageal Pressure; SniffPgas: sniff gastric pressure; SniffPdi: sniff transdiaphragmatic Pressure; Pgas cough: gastric pressure during a maximal cough.