

**SEPN1 related myopathies: Clinical course in a large cohort of patients**

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**Abstract:**

Objective: To assess the clinical course and genotype/ phenotype correlations in patients affected by selenoprotein related myopathy (SEPN1-RM) due to *selenoprotein NI* gene mutations for a retrospective cross-sectional study.

Methods: Forty-one patients aged 1-60 years were included. Clinical data including scoliosis, respiratory function and growth measurements were collected by case note review.

Results: Mean age of onset was 2.7 years, ranging from birth to the second decade of life. All but two remained independently ambulant: one lost ambulation at age 5 years and another in his late fifties. The mean age of starting nocturnal non-invasive ventilation (NIV) was 14.3 years. One child required full time NIV at the age of one year while in two cases NIV was started at 33 years. Two patients died from respiratory failure at the age of 10 and 22 years respectively. The mean age of scoliosis onset was 10 years, in most cases preceded by rigidity of the spine. Fourteen patients had successful spinal surgery (mean age 13.9 years). Twenty-one were underweight; however overt feeding difficulties were not a feature.

Conclusions: This study describes the largest population affected by SEPN1-RM reported so far. Our findings show that the spectrum of severity is wider than previously reported. Respiratory insufficiency generally develops by 14 years but may occur as early as in infancy or not until the fourth decade. Motor abilities remain essentially static over time even in patients with early presentation. Most adult patients remain ambulant and fully employed.

## Introduction

Mutations in the *Selenoprotein N1 (SEPN1)* have been described in patients who share key clinical features including early axial onset, rigidity of the spine, early and life threatening respiratory insufficiency with a relatively slow course and limited evidence of progressive muscle damage, as indicated by normal or only mildly increased serum CK levels<sup>(1-3)</sup>. *SEPN1* mutations, initially reported in patients whose muscle showed mild dystrophic changes, have subsequently also been found in patients in whom the main histopathological features were either multiminicores, congenital fiber-type disproportion, or myopathy with Mallory-body like inclusions<sup>(4-7)</sup>. Clinically, there is a significant overlap among these forms, and the term SEPN1-related myopathy (SEPN1-RM) has now been suggested when referring to these conditions<sup>(3-5, 8-12)</sup>.

Recessive missense or nonsense mutations of *SEPN1*, located on chromosome 1p36-13<sup>(5)</sup> have been described in several small series of patients without a clear correlation between genotype and clinical course or pathological findings<sup>(3, 4, 13)</sup>.

Although the precise function of SEPN1 protein is uncertain, recent studies suggest a role in the physiological redox-related calcium homeostasis and cell protection against oxidative stress<sup>(14, 15)</sup>.

While *SEPN1* mutations in patients with the various histopathological phenotypes<sup>(2, 4, 5, 13, 16)</sup> have been described, no systematic study correlating these findings in a large cohort of SEPN1-RM patients has been reported.

In this study, we investigated the clinical course and genotype/ phenotype correlations in forty-one SEPN1-RM patients, including children, adolescents and

adults, focusing on the age of presentation, functional mobility impairment and major events such as age when respiratory support was initiated, respiratory involvement, spinal surgery and survival.

### **Subjects and Methods**

This was a retrospective cross sectional study of 41 patients with molecularly confirmed SEPN1-RM. Data were collected by reviewing the case notes of patients followed at the Dubowitz Neuromuscular Centre in London UK (18/41), or from other centers who referred muscle biopsy and/or DNA samples to our National Commissioning Group service and provided clinical information using a structured questionnaire (23/41). Follow-up data was provided by the referring clinicians involved.

The following data were collected: age of presentation, maximal serum CK level documented, mobility and motor functional ability at the time of the survey, presence or absence of rigidity of the spine and other contractures, presence and severity of scoliosis and age at spinal surgery if performed, respiratory function including forced vital capacity (FVC) measurement and results of overnight oxygen saturation monitoring studies, the age at initiation of nocturnal non-invasive ventilation (NIV), weight gain, heart function, survival, muscle biopsy features, and genetic analysis. Respiratory intervention with nocturnal NIV was established following clinical evaluation together with the evidence of nocturnal hypercarbia<sup>(17)</sup>

Genetic analysis

Genomic DNA was extracted from peripheral blood leucocytes according to standard procedures and the *Selenoprotein N 1* exons were sequenced from genomic DNA. Mutations are listed in **supplementary table 1**.

#### Statistical analysis

Descriptive statistics were used for clinical items with mean, median and standard deviation. Kaplan-Meier curve was performed with the use of GraphPad Prism 4 software. The relationship between FVC% and age was estimated using a simple linear regression.

#### Results

Forty-one patients with SEPN1-RM aged between 1 and 60 years (mean 19.2 years) were included in the study. Four patients had consanguineous parents (**supplementary table 1**). The clinical data reported in table 1 relate to the last follow up assessment. **Supplementary table 2** shows an overview of the main clinical features according to age cohorts.

#### Onset of symptoms

The mean age of onset of symptoms was 2.7 years (median 1.5, SD 3.2), ranging from birth to the second decade. Fifteen patients (36.5%) had a congenital presentation with a variable combination of hypotonia (11/15), torticollis (1/15), feeding difficulties (2/15) and recurrent chest infections (1/15). In 19 patients (46%) the presentation was between 6 months and 5 years of age with delayed motor milestones or gross motor difficulties, subdivided in the following categories: 8/19 (42%) delayed ability to sit unsupported, 6/19 (31.5%) delayed walking (after 18 months of age) and 5/19 (26%) presented with difficulty

running or frequent falls. In 3 patients (7.3%) the presentation was between 6 to 10 years of age with scoliosis (1/3), or easy fatigability (2/3). Another two patients were first referred at the age of seven years for walking and running difficulties. Two patients (4.8%) presented at 13 years of age with back stiffness and general muscle wasting with weakness.

#### Creatine Kinase

CK serum level was available in 37/41 patients and was within the normal range (upper level 150 U/L) in 29/37 (73%); minimally elevated (ranged 156-283 U/L) in 6/37 (16%) and markedly elevated (1400 U/L at eight years) in one patient (7, table 1). Another patient, a 5-year-old girl (40, [supplementary table 1](#)) had a value of 2459 UI/L but she was also a Duchenne muscular dystrophy carrier, with a nonsense mutation in the dystrophin gene (c.2348A>C).

#### Functional abilities

All patients acquired independent ambulation. All but two patients remain fully ambulant and able to walk independently indoors and outdoors. However one patient became wheelchair dependent in his late fifties, four patients required a wheelchair for long distances, and one patient aged 5 years needed help to self stand and take few steps. Despite the presence of motor difficulties such as climbing stairs in 24 of 39 (62%) ambulant cases, functional abilities did not deteriorate during follow-up in most patients of our cohort (85% of cases) ([supplementary tables 1 and 2](#)).

#### Joint contractures

Joint contractures were present in 26 patients (63%) at a mean age of 10.4 years (median 8 and SD 7.2); Achilles tendon (17/25) and elbow (12/25) contractures were most commonly observed, followed by long finger flexor contractures.

Two patients had finger contractures at birth; in 7 patients distal laxity was noted together with joint contractures. In 2 patients isolated distal joint laxity was a prominent feature.

#### Respiratory function

FVC data were available from 26 patients older than 5 years. Figure 1a shows the correlation between FVC% with increasing age. All patients except one had FVC values below 80% of that predicted for height. The linear correlation showed a drop of FVC of 1.1% per year (95% CI, 0.12 to 2.1),  $p=0.029$ . Individual values and the 95% confidence interval are given in Figure 1a.

Data on overnight oxygen saturation studies were available in 37/41 cases. In 32 of the 37 (86%) some abnormalities were found at a mean age of 13.2 years (SD 6.5 and median 13.2), requiring nocturnal NIV in 27/32, at a mean age of 13.9 years (median 14; SD 7). Of the 4 cases without a sleep study result, three declined scheduled regular respiratory follow-up (21, 33 and 36 [supplementary table 1](#)) in the remaining one the study is awaited (30, [supplementary table 1](#)).

The need for nocturnal NIV increased with age, as at the age of 15 years 50% of cases needed ventilatory support, while at 20 years the need of ventilatory support was increased to 75% of cases (Figure 1b). The youngest ventilated patient was aged 1 year and two other patients required ventilation at the age of 5 years (in one of them the first abnormal sleep study was documented at the age of



four). Two patients (4.8%) were not ventilated in the fourth decade (1 and 3, **supplementary table 1**). The mean FVC value when starting NIV was 29.6% (SD 10.8). There was no apparent increased dependency on NIV with age.

### Spine

Scoliosis developed in 28 patients (70%) at a mean age of 10.2 years (Median 10 and SD 3.8); in 4/28 it developed before five years but 14/28 (50%) patients were older than 10 years. In most cases rigidity of the spine preceded the scoliosis with a mean age of onset of 8.6 years (Median 8 and SD 4.3). **Spinal surgery was proposed when patients had a progressive curvature which Cobb angle exceeded 50 degrees<sup>(18)</sup>**. A spinal fusion was performed in 14 patients (34%) at a mean age of 13.9 years (median 14.9 and SD 3.7) with only one child requiring surgery at the age of 3 years. **The duration of follow-up post-surgery ranged between 1 to 26 years (mean 7.9)**. All the operated patients remained fully ambulant after the surgery with the exception of the one operated at 3 years who required a wheelchair for long distances at the age of 11 years. In 5/14 operated cases (36%) a temporary improvement of the FVC was noted about six months to one year after surgery, with a mean FVC improvement of 11% (SD 5.4).

### Cardiac involvement

Thirty-two of 41 patients underwent cardiac assessment and 27/32 had normal ECG and echocardiogram (84%), although mild right ventricular hypertrophy/mild pulmonary hypertension was found in the remaining five patients (16%).

### Weight gain

Weight measurement was available in 35 patients. Twenty of the 35 (57%) were underweight (<3<sup>rd</sup> percentile) and 3 (8.5%) were above the 97<sup>th</sup> centile. Those patients with the lowest weight percentile subsequently followed this centile with no drop in growth velocity. There was no obvious association between weight and level of ability. None reported significant feeding difficulties but one patient (27, [supplementary table 1](#)) required gastrostomy with fundoplication for gastro-oesophageal reflux at the age of one year. Three cases (9, 25 and 30, [supplementary table 1](#)) were prescribed food supplements, which resulted in effective weight maintenance.

#### Survival

Two patients died from respiratory failure at the age of 10 years and 22 years. The first patient (21, [supplementary table 1](#)) was a girl with obesity and hepatic steatosis who failed to attend her scheduled respiratory follow-up despite her FVC being abnormal at 36% at the age of 10 years.

The second patient (33, [supplementary table 1](#)) declined the scheduled regular respiratory follow-up and died suddenly at home at the age of 22 years. A post-mortem examination showed a mild right ventricular hypertrophy.

#### Muscle biopsy

A muscle biopsy was performed in 34/41 patients. The main histological changes, reported by our pathologist in 10/34 cases and by the referring pathologists in the remaining cases ([supplementary table 1](#)), included cores/multiminicores (19/34, 55% of cases, in association with marked fibrosis in one case); non specific myopathic changes in eight cases (24%), including two

cases with excess fibrosis, one of whom was also a carrier of Duchenne muscular dystrophy; type 1 predominance in 7/34 (21%) patients including one case presenting in association with minicores; the presence of Mallory bodies was reported in one patient.

#### Genetic analysis

Genomic sequencing revealed 14 previously undescribed *SEPNI* mutations. The distribution of mutations is shown in table 1; 48% are missense, 18% splice site, 28% small deletions/insertions including a 92bp deletion extending from exon 1 in the 5'UTR. We observed a cluster of mutations in exons 1, 6, 7 and 10.

Twenty-one of 41 patients carried a homozygous mutation; the remaining 20 were compound heterozygous for the identified mutations. Two patients (11 and 19, [supplementary table 1](#)) had in compound heterozygous state the c.1397 G>A mutation in the selenocysteine redefinition element (SRE)<sup>(8)</sup>. The selenocysteine incorporation codon which is located in exon 10 may also be involved in four additional patients (4,5,12, 23, [supplementary table 1](#)) who have splice site mutations at the splice donor site of exon 9. Although the effect of splice site mutations needs to be verified with by RNA analysis, these mutations are most likely to affect the splicing of exon 10 and induce a frameshift. Several patients with homozygous mutations affecting the SEPNI start codon, in whom no SEPNI is predicted to be produced, have relatively mild phenotypes (cases 2, 7, 16, 26, 39); however 2 individuals (29 and 37) are more severely affected, needing a wheelchair for long distances ([supplementary table 1](#)). We did not observe a clear correlation between genotype and phenotype, including the

muscle biopsy findings. The c.943 G>A mutation described before<sup>(4, 7, 19)</sup> was present in 11 patients.

## **Discussion**

*SEPN1* mutations in patients with rigid spine have been described in association with dystrophic changes on muscle biopsy since 1998 and subsequently with multiminicores, congenital fibre type disproportion, and Mallory-bodies inclusions in several studies<sup>(2, 4, 5, 13, 16)</sup>. Most of the previous studies reported small number of patients associated with each of these forms and showed remarkable clinical homogeneity<sup>(2, 4, 5, 13, 16)</sup>. The age of the patients reported so far ranged between one and forty-one years<sup>(1-4, 13, 19, 20)</sup>. In the present study, we report a larger number of SEPN1-RM patients of wider age range, irrespective of the clinic-pathological phenotype. Our cross-sectional data provides additional information on the spectrum of clinical features in this condition. In agreement with previous studies<sup>(2, 3, 5, 14)</sup> we found that in most patients the onset of clinical signs was in the first few years of life with nineteen of them having delayed milestones or gross motor difficulties detected before the age of 5 years. In a minority of cases however (2/41) there was no concern until the second decade of life.

With few exceptions, all our patients maintained ambulation. Of the three cases who were older than 40, all remained ambulant and fully active with the exception of one case who needed a wheelchair for outdoors in the sixth decade followed by progression of weakness in the late fifties. Few patients (9.7%) had

difficulties walking outdoors for long distances; this occurred in the first decade (2 cases) and in the second decade (2 more cases), due to progressive scoliosis and weakness **without no specific precipitating factors**. Only one patient (27, **supplementary table 1**), with a congenital presentation, was unable to walk without help at 5 years, while several other patients with congenital onset were fully ambulant in adulthood, suggesting that the clinical course severity is independent of the age of onset.

Joint contractures were found in most cases (63%), most commonly in Achilles tendons and elbows and less frequently in the long finger flexors. As previously noted, contractures are neither a presenting feature<sup>(2-4)</sup> nor a significantly progressive factor in the condition, with the exception of the spinal rigidity.

Scoliosis was frequent (70%), developing at a mean age of 10.2 years, often preceded by spinal rigidity. As a result of severe scoliosis about one third of the patients had a spinal fusion at a mean age of 13.9 years (**supplementary table 1**); the surgery was well tolerated in all of them with no deterioration of motor or respiratory function after surgery.

FVC values were abnormal in all patients, except one around 8 years, from the age of 5 years, which is the earliest age at which FVC can be reliably measured in our experience. Sleep studies were found to be abnormal at a mean age of 13.2 years, anticipating the need for nocturnal NIV which became necessary in 66% of our patients during the second decade of life at a mean age of 13.9 years. It is of note that in two patients abnormal nocturnal oxygen saturation monitoring was present as early as two and four years of age respectively, suggesting that sleep

studies should be performed regularly even in young children. At the other end of the spectrum, two patients started NNIV only at the age of 33 years after an episode of acute respiratory failure. Such a delayed onset of respiratory insufficiency is unusual for this condition as only one case of SEPN1-RM presenting as cor pulmonale at the age of 26 years has previously been reported<sup>(15)</sup>.

In our cohort there was no clear progressive deterioration of respiratory function following the introduction of NNIV and FVC values were found to be essentially stable after the second decade of life. **Our data also confirm that heart function is usually not altered in SEPN1-RM patients; in a few cases we found evidence of mild right ventricular hypertrophy or mild pulmonary hypertension, likely secondary to the respiratory insufficiency, which improved following commencing NIV**<sup>(2-4, 13, 19)</sup>.

Weight was below the 3<sup>rd</sup> centile in 57% of the patients in whom accurate measurements were available. This is in keeping with similar previous findings<sup>(4)</sup> suggesting that this is a core feature, despite there being no obvious swallowing or chewing difficulties. This aspect should be considered in the long-term management as gastrostomy is only rarely necessary but supplementary food could be offered to maintain weight, if appropriate. On the other hand, 3/34 cases (9%) were obese, but this did not have any effect on the severity of their disease<sup>(5)</sup>.

We found no clear correlation between the clinical features and the main muscle pathology findings; the distribution of the various histopathological subtypes

largely reflects that previously described<sup>(2, 4, 5, 13, 16)</sup>. We also did not observe a clear genotype and phenotype correlation. There was an equal distribution of patients carrying homozygous and compound heterozygous mutations, with 14 novel *SEPN1* mutations ([supplementary table 1](#)). The c.943 G>A mutation described earlier<sup>(4, 7, 19)</sup> was observed in 11 patients, suggesting that this could be a founder mutation.

In conclusion, our study expands the spectrum of clinical findings associated with *SEPN1* mutations, both regarding the range of severity of the disease and age of onset and the long-term functional outcome. Our study suggests that the course of motor function is essentially stable in the majority of patients, although in 15% of cases there was a clear progression of weakness and functional disability.

Furthermore this study expands the spectrum of respiratory involvement as, in three cases, respiratory insufficiency was already present in the first years of life while, at the other end of the spectrum, we found patients who only required nocturnal NIV in the fourth decade. Our results also confirmed that initiation of nocturnal NIV is very effective and that NIV was invariably required only at night.

One of the limitations of the study is that the data were not prospectively collected. Nevertheless, the large number of cases and their wide age range is an important step forward in defining the natural history of *SEPN1*-RM. This provides valuable information for counseling patients, for improving management and standards of care, but also provides useful information on the progression of this disorder which may be used for future clinical trials, as drugs

such as N-acetylcysteine (NAC), able to protect patient cells from oxidative stress induced cell death, are considered for clinical trials<sup>(14, 15)</sup>.

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### Figure Legends

Figure 1 A: Progression of FVC with age

The relationship between FVC% and age shows the decrease of the FVC% in relation to the age in years using a simple linear regression. (95% CI, 0.12 to 2.1),  $p=0.029$ . Individual values in blue dots and the 95% confidence interval indicated by the dashed line. The slope given is in figure with  $R^2$  0.07. Several patients had repeated FVC at a different ages.

Figure 1 B: Kaplan–Meier curve showing ventilation-free probability.