ARTICLE

The clinical, histologic, and genotypic spectrum of *SEPN1*-related myopathy

A case series

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Abstract

Objective

To clarify the prevalence, long-term natural history, and severity determinants of *SEPN1*-related myopathy (SEPN1-RM), we analyzed a large international case series.

Methods

Retrospective clinical, histologic, and genetic analysis of 132 pediatric and adult patients (2–58 years) followed up for several decades.

Results

The clinical phenotype was marked by severe axial muscle weakness, spinal rigidity, and scoliosis (86.1%, from 8.9 ± 4 years), with relatively preserved limb strength and previously unreported ophthalmoparesis in severe cases. All patients developed respiratory failure (from 10.1±6 years), 81.7% requiring ventilation while ambulant. Histopathologically, 79 muscle biopsies showed large variability, partly determined by site of biopsy and age. Multi-minicores were the most common lesion (59.5%), often associated with mild dystrophic features and occasionally with eosinophilic inclusions. Identification of 65 *SEPN1* mutations, including 32

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Glossary

BMI = body mass index; **CNV** = copy number variation; **FVC** = forced vital capacity; **MH** = malignant hyperthermia; **MRC** = Medical Research Council; **NGS** = next-generation sequencing; **NMD** = nonsense-mediated decay; **SEPN1-RM** = SEPN1-related myopathy.

novel ones and the first pathogenic copy number variation, unveiled exon 1 as the main mutational hotspot and revealed the first genotype–phenotype correlations, bi-allelic null mutations being significantly associated with disease severity (p = 0.017). SEPN1-RM was more severe and progressive than previously thought, leading to loss of ambulation in 10% of cases, systematic functional decline from the end of the third decade, and reduced lifespan even in mild cases. The main prognosis determinants were scoliosis/respiratory management, *SEPN1* mutations, and body mass abnormalities, which correlated with disease severity. We propose a set of severity criteria, provide quantitative data for outcome identification, and establish a need for age stratification.

Conclusion

Our results inform clinical practice, improving diagnosis and management, and represent a major breakthrough for clinical trial readiness in this not so rare disease.

Recent progress is bringing congenital myopathies to the clinical trial stage, but for the forms associated with mutations in the selenoprotein N gene (*SEPN1 or SELENON*, MIM*606210), clinical trial readiness is lagging behind. *SEPN1* mutations were first associated with rigid spine muscular dystrophy[1–3] and shortly after with multi-minicore disease,[4] congenital fiber type disproportion,[5] and desmin-related myopathy with Mallory body–like inclusions.[6–9] These 4 autosomal recessive conditions share so many clinical and molecular features that they are considered the same disorder, which we termed *SEPN1*-related myopathy (SEPN1-RM).[4]

Selenoprotein N, an endoplasmic reticulum glycoprotein, has a potentially calcium-binding EF-hand motif and a selenocysteine-containing domain with putative reductase activity. SEPN1 plays a key role in redox-based calcium homeostasis[10,11] and cell protection against oxidative and endoplasmic reticulum stress.[10,12–14] These pathways are drug-targetable, and some compounds effectively rescue the SELENON-devoid cell phenotype ex vivo.[12] However, SEPN1-RM clinical trial readiness is hindered by the lack of validated biomarkers and the scarcity of quantitative data on its phenotypical spectrum, long-term natural history,[4,7,9] disease progression, or prognosis determinants. SEPN1-RM is considered to be very slowly progressive, but the impact of age has never been analyzed, and phenotype–genotype correlations are unclear. Finally, although SEPN1-RM is considered an ultrarare disease, its prevalence is unknown. This global situation complicates patient diagnosis and management and hampers clinical trial implementation.

We report the largest international SEPN1-RM series, thus informing diagnosis and management and paving the way for clinical trial readiness.

Methods

Standard protocol approvals, registrations, and patient consents

Written informed consent according to local ethical committees in all participating centers was obtained for all patients. Clinical and genetic data were anonymized and entered into a secured database accessible only to the first and last authors.

Patients

We included 132 patients with *SEPN1* mutations identified between 2001 and 2017. Thirty-one were reported previously.[3,4,6,9]

Clinical data were analyzed retrospectively according to a standardized form completed by the referent clinicians, except for 31 cases from whom only genetic information was available. The frequency of each finding was calculated over the number of patients from whom these data were available.

Standard blood test results were collected from 76 patients, and in 6, serum selenium levels, serum and erythrocyte glutathione peroxidase, lactate, pyruvate, thyroid hormones, and carnitine were quantified. EMG and brain MRI/CT scan were performed in 24 and 27 patients, respectively. Muscle MRIs in 5 patients were reported previously.[15]

Skeletal muscle biopsy

We reviewed 79 muscle biopsies (light and electron microscopy) or histopathologic reports. Muscle biopsy site, known in 43 patients (45 biopsies), was deltoid (n = 22, 48.9%), quadriceps (n = 17, 37.8%), biceps brachialis (n = 2, 4.3%), gastrocnemius (n = 2, 4.3%), or abdominal muscles (n = 2, 4.3%).

Genotyping

SEPN1/SELENON was analyzed on genomic DNA from peripheral blood using Sanger sequencing[4] or next-generation

sequencing (NGS)–based gene panels.[16] Variants were reported according to Human Genome Variation Society recommendations (varnomen.hgvs.org/) using the complete *SEPN1/SELENON* transcript (NM_020451.2; NP_065184.2). Genome Aggregation (gnomad.broadinstitute.org/) and Clinvar (ncbi.nlm.nih.gov/clinvar/) databases were interrogated to identify previously reported mutations and to determine variant frequency in the population. Alamut-Batch-UI v1.11 (Interactive Biosoftware, North Seattle, WA) was used to predict variant impact.

Statistical analysis

Data were analyzed with SPSS Statistics version 22.0 (Armonk, NY: IBM Corp). Results are expressed as mean ± SD. Groups were compared using the Welch *t* test or Mann-Whitney-Wilcoxon test for continuous variables and Pearson χ^2 test for categorical variables, as appropriate. A 2-sided *p* value ≤ 0.05 was considered statistically significant. Kaplan-Meier was used to analyze ventilation-free probability.

Data availability

The anonymized raw data supporting our findings are available upon request.

Results

The disease affected female (50.8%) and male (49.2%) patients similarly. Patients were aged 2–58 years at last examination (mean 18.2 ± 11.8 years). Follow-up ranged from 8 months to 25 years.

Consanguinity was confirmed in 30 families and probable in 3. Fourteen families reported early deaths of 18 genetically undiagnosed members (not included) at ages 4–19 years, mainly due to untreated respiratory failure or during their sleep. Eight of them showed axial weakness and progressive scoliosis or rigid spine, 4 had clinical myopathic signs, and 1 had a dystrophic muscle biopsy.

Clinical phenotype

Clinical features are summarized in table 1.

Onset and first signs: an infantile myopathy, often underrecognized

First signs were noticed before the age of 15 years in all patients, and within the first 2 years in 84.7% (mean 18.2 ± 29.8 months).

Delayed motor development was the most common presenting sign (81.4%). Poor head control, the referral abnormality in 57.7% patients, was almost systematically retrieved by parents when retrospectively asked. Independent ambulation was acquired by all but one severely affected patient, often (59.3%) before 18 months (mean 17.6 ± 4.9 months).

Pregnancy information was retrieved for 29 patients. Most lsb were normal, with exceptional cases of preterm deliveries (n = 2), reduced fetal movements (n = 3), or intrauterine growth retardation (n = 2). Neonatal hypotonia was reported in one third of cases. Other early signs were feeding difficulties or failure to thrive (17.5%) and respiratory problems (7.2%). Four patients presented with early-onset scoliosis, hyperlordosis, or rigid spine and 16 were referred for unspecified muscular weakness and hypotonia, sometimes associated with abnormal gait, inability to run, difficulty climbing stairs, or frequent falls. Arthrogryposis or congenital contractures were absent, excepting congenital torticollis in one patient.

One patient was diagnosed at 31 years, when prolonged bed rest after a stroke (carotid dissection) caused hypercapnic coma, revealing chronic diaphragmatic and respiratory failure. Retrospectively, she reported mild axial and proximal weakness from early childhood.

The axial connection: a recognizable, homogeneous phenotype

All patients shared a remarkably consistent and recognizable phenotype (figure 1).

In the first decade, patients typically showed a particular facial appearance, long slender neck, flat retracted thorax, spinal rigidity, and axial weakness but preserved ambulation. Most had poor head control, were never able to lift their head from supine, and had to sit up from supine by rolling over and pushing on their arms. However, they were typically able to climb stairs and walk outdoors unsupported, limited mainly by fatigue. Sports performance was usually poor, cervical rigidity preventing some patients from rolling forward.

Amyotrophy involved preferentially neck and trunk muscles (particularly sternocleidomastoid), deltoid, the inner thigh compartment ("bracket-like thighs"), and distal forearm and leg muscles. Typical facies (figure 1B) was associated with mild to moderate facial weakness, high-arched palate, and nasal high-pitched voice. Muscle weakness was severe in neck flexors and in abdominal muscles (0–3, Medical Research Council [MRC] scale), with relatively well-preserved neck extensors. Limb weakness was usually milder and predominantly proximal (MRC 3–4 in scapular girdle, 2–3 in psoas, glutei, and adductor muscles). Quadriceps strength was often normal or mildly reduced (MRC 4–5) and distal weakness was present in the most severe cases. Deep tendon reflexes were invariably diminished or absent.

Rigid spine was present in 87.8%, generally before the age of 10 years (mean 8.1 ± 3.9 years) and reported as early as in the first year. Severe contractures of neck extensors and dorsal paraspinal muscles caused cervicodorsal rigidity, bending forward remaining possible due to relative preservation of lumbar spine mobility. Loss of dorsal kyphosis or dorsal lordosis caused reduced anteroposterior thorax diameter. Pectoralis major and intercostal muscle retractions contributed to thoracic deformities and poor mobility.

The full phenotype usually manifested around puberty, with the development of scoliosis, the detection of respiratory

Table 1 Main clinical features reported by clinicians

	No. of cases (%)[a]
Age at first noticed signs (n = 98)	
Birth to 6 months	46 (46.94)
From 6 months to 1 year	25 (25.51)
From 1 to 2 years	12 (12.24)
From 2 to 8 years	12 (12.24)
Older than 8 years	3 (3.06)
First/referral signs (n = 97)	
Neonatal hypotonia	32 (32.99)
Delayed motor milestones	79 (81.44)
Poor head control (head lag)	56 (57.73)
Delayed gait acquisition	31 (31.96)
Abnormal gait, inability to run, or frequent falls	34 (35.05)
Nonspecified weakness/hypotonia	16 (16.49)
Difficulty feeding/failure to thrive	17 (17.53)
Early respiratory problems (e.g., neonatal respiratory distress, recurrent respiratory infections)	7 (7.22)
Scoliosis, hyperlordosis, or rigid spine	4 (4.12)
Hypercapnic coma	1 (1.03)
Muscle weakness distribution (n = 80)	
Predominantly axial + proximal	80 (100)
Significant distal involvement	11 (13.75)
Facial muscle weakness (n = 60)	48 (80)
High-arched palate (n = 58)	36 (62.07)
High-pitched/nasal voice (n = 67)	52 (77.61)
Mild ptosis (n = 79)	6 (7.59)
Ophthalmoparesis (n = 79)	3 (3.79)
Rigid spine (n = 98)	86 (87.75)
Scoliosis (n = 101)	87 (86.14)
Arthrodesis	32 (36.78)
Thoracic deformities (n = 57)	41 (71.93)
Flat thorax	18 (31.58)
Pectus excavatum	15 (26.32)
Pectus carinatum	1 (1.75)
Nonspecified	7 (12.28)
Respiratory involvement (n = 100)	94 (94)
Not properly evaluated (<6 y)	6 (6)
Age at detection, y (n = 62)	
0–9	29 (46.77)
10–15	27 (43.54)
>15	6 (9.67)
FVC % (n = 69)[a]	
≥65%	2 (2.89)
50%–65%	8 (11.59)
30%–50%	34 (49.28)
<30%	25 (36.23)
Assisted ventilation	77 (81.91)
Cardiac abnormalities (n = 76)[a]	12 (15.79)
Cor pulmonale	4 (5.26)
Increased RV systolic pressure	1 (1.32)
Mitral valve prolapse	3 (3.95)
Other valvular abnormalities	3 (3.95)
Dilated cardiomyopathy	1 (1.32)
Joint contractures/hyperlaxity (n = 87)	56 (64.37)
Only axial (spinal) contractures	10 (11.49)
Mild to moderate axial + limb contractures	37 (42.53)
Severe axial + upper and lower limbs	9 (10.34)
Mild distal hyperlaxity	21 (24.14)
Distal hyperlaxity + contractures	16 (18.39)
Other clinical features	
Foot deformities	14
Equinovarus foot	7
Flat feet	7
Hip dysplasia	2
Skin abnormalities	8
Trunk acne	3
Nevus flammeus	2
Follicular hyperkeratosis	1
Facial angioma	1
Thoracic angioma	1
Xerosis	1
Strabismus	4
Deglutition problems	15
Genitourinary involvement	6
Gastrointestinal involvement	3
Gastroesophageal reflux	1

Continued

Table 1 Main clinical features reported by clinicians *(continued)*

	No. of cases (%)[a]
Bulbar ulcer	1
Steatorrhea	1
Mild learning difficulties	3
Dysarthria	3
Congenital torticollis	1
Progression of muscle weakness (n = 77)	
Stable/stationary	45 (58.44)
Slowly progressive	32 (41.56)
Rapidly progressive	2 (2.59)
Wheelchair-bound patients	8
Deaths	6

Abbreviations: FVC = forced vital capacity; RV = right ventricle.
Patients of a wide age range (2–56 years) have been included. Younger patients may not have developed all the characteristic features yet.
[a] The denominator for percentage calculations was the number of cases with available data for each item.

failure, a further drop in weight curves, and, in some cases, limb contractures, although all the former appeared earlier in severe cases (figures 1B and 2).

Scoliosis appeared at a mean age of 8.9 ± 4.0 years (10.4 ± 3.6 in boys, 7.9 ± 3.9 in girls), was present in 86.1% of all cases and in 93.8% of those aged more than 13 years. SEPN1-RM scoliosis is peculiar and recognizable because of dorsal hyperlordosis (leading to scapular pseudo-winging) and important lateral trunk shift contrasting with balanced hips (figure 2B.a.). Adapted bracing helped delay surgery until the end of puberty, but did not prevent scoliosis progression. Arthrodesis was performed in 32 postpubertal patients at ages 10–17 years (mean 13.5 ± 1.9 years). Scoliosis usually remained clinically and radiologically stable after extensive spinal fusion.

Although birthweight was often normal, typically body weight decreased drastically around puberty, leading to loss of subcutaneous adipose tissue and a cachexia-like appearance (figures 1 and 2). Most (72.7%) patients were under the 4th weight percentile, and the mean body mass index (BMI) in adults was 16.9 ± 4.0 (women 16.5 ± 4.3, men 17.4 ± 3.6). Two patients were overweight and 2 were obese since childhood; these 4 patients had severe forms of the disease, with major respiratory failure and early loss of ambulation.

Limb joint contractures, usually mild in children, were reported in 64.4% of cases, involving the Achilles tendon (57.4%), hip flexors (50%), elbows (35.2%), or knees (31.5%). Only 9 children showed a more contractile phenotype with severe axial and limb contractures. Finger flexor contractures upon wrist extension or, less often, limitation of mouth opening appeared with age. Distal hyperlaxity was reported in 21 patients and associated with joint contractures in 16 (figure 3).

Mild limitation of superior vertical eye movements was not uncommon when specifically examined. We identified previously unreported clear ophthalmoparesis in 3 severely affected patients. Oculomotor abnormalities became more obvious with age. Strabismus and mild ptosis were observed in 4 and 6 patients, respectively.

Respiratory involvement

Respiratory involvement was strikingly disproportionate to limb weakness, most patients requiring assisted ventilation while ambulant. Both weakness of the respiratory and accessory respiratory muscles and thoracic deformities contributed to respiratory failure. Dorsal spine lordosis and rigidity led to severely reduced thorax anteroposterior diameter, bronchial compression, or subsequent atelectasis.

Restrictive hypoxemic and hypercapnic respiratory failure was present in 93% of cases (from 10.06 ± 6.10 years). Forced vital capacity (FVC) was in most patients between 20% and 40% of predicted values (36.47 ± 12.31) at last survey (figure 4). Diaphragmatic weakness (>10% FVC decrease in supine from baseline sitting position) was reported in 30 patients. Polysomnography detected nocturnal hypoventilation (92.9%) from early ages, even in patients with relatively preserved FVC and no daytime respiratory signs. The 3 youngest patients studied had polysomnographic values within normal range at 4 years but abnormalities requiring ventilation at 5.5 years.

A total of 81.9% of cases had assisted ventilation, from mean age of 14.14 ± 7.89 years (3–49 years). Most required nocturnal noninvasive ventilation; 12 had a tracheotomy.

Compressive bracing led to hypercapnic coma in one patient. Four patients developed cor pulmonale and one had isolated increase of right ventricular systolic pressure secondary to respiratory failure. All improved with instauration or adjustment of assisted ventilation.

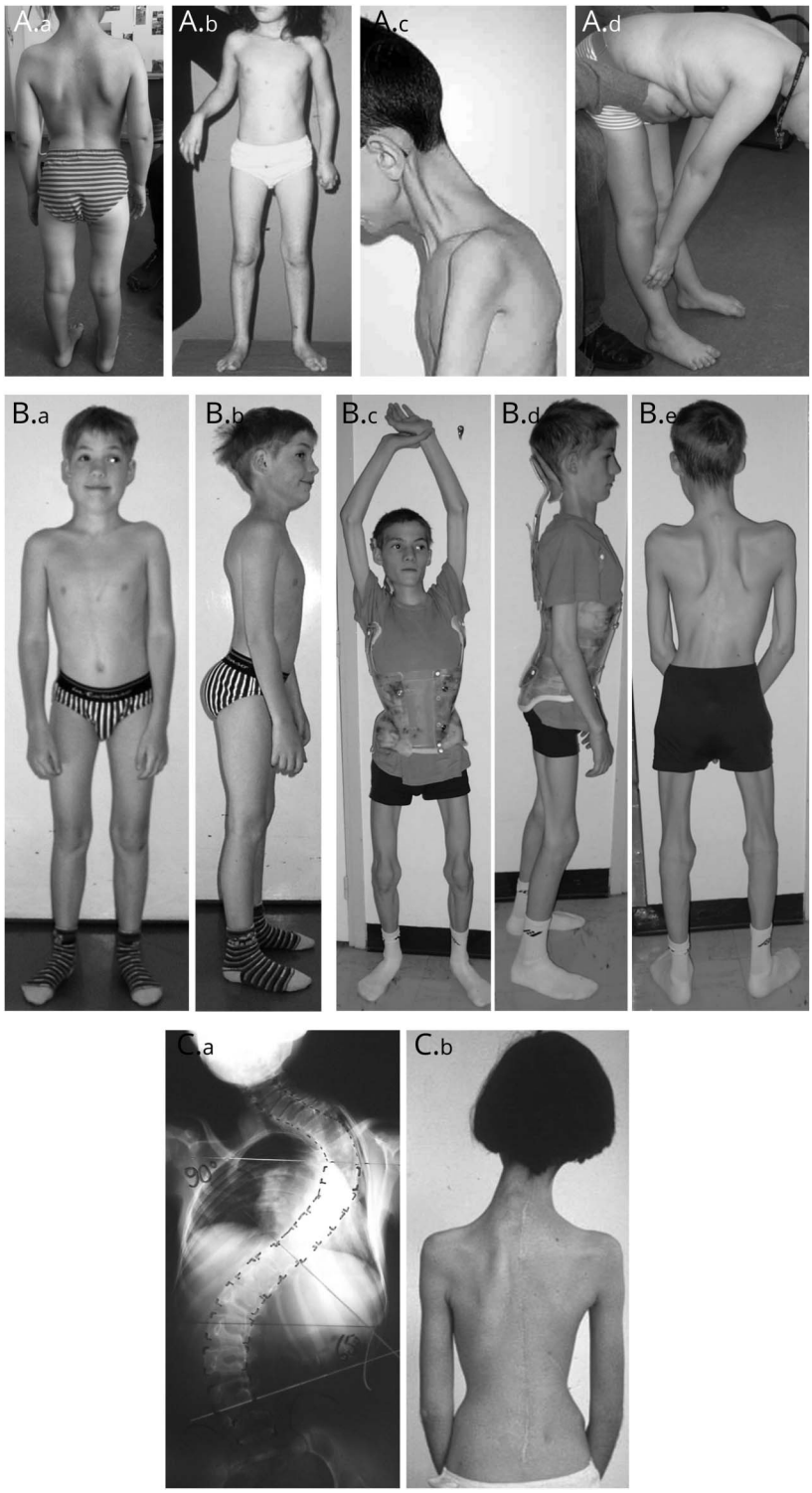
Other features

One patient with idiopathic cardiomyopathy family history developed dilated cardiomyopathy at 42 years. Fifteen patients developed swallowing difficulties. Gastrointestinal involvement, genitourinary disorders, or nonspecific skin abnormalities were reported in a minority of patients. One patient had a cerebral venous thrombosis at age 38. No patient had intellectual disability or CNS involvement.

Ancillary tests

Creatine kinase levels were normal or mildly elevated (34–453 UI/L, 5 cases ≥ 3 × N). Two patients had normal in vitro

Figure 1 Distinctive clinical signs



(A) The clinical phenotype in early childhood was recognizable by predominantly axial weakness, deltoid and inner thigh amyotrophy ("bracket-like thighs") (A.a and A.b) and spinal rigidity identifiable upon specific examination (A.c and A.d). Axial rigidity was typically more prominent in the cervicodorsal spine (A.c and A.d), with relative or full preservation of lumbar spine flexion (A.d). (B) Typical moderate patient at ages 11 (B.a and B.b) and 14 years (B.c–B.e). Often subtle until late childhood, the full phenotype usually became apparent around puberty. Body weight decreased dramatically, leading in some cases to an apparent loss of subcutaneous adipose tissue (lower limbs in B.c and B.d) and a cachexia phenotype. Most patients developed scoliosis (B.e), which required adapted bracing to avoid thorax compression (Garchois brace, B.c and B.d). SEPN1-RM scoliosis is recognizable due to dorsal lordosis leading to pseudo-scapular winging, lateral trunk deviation with compensatory contralateral neck shift, and horizontally aligned hips. (C) Scoliosis progression despite bracing often required arthrodesis (moderately affected patient before [C.a] and after [C.b] spinal fusion).

contracture tests for malignant hyperthermia (MH) susceptibility and none had history of MH. EMG disclosed small amplitude, brief, polyphasic action potentials and normal nerve conduction. Brain MRI or CT were normal aside from arachnoid cysts (n = 2) or Chiari malformation type 1 (n = 1).

A previous review of whole-body MRI, including 5 patients from this series, revealed a homogeneous and recognizable SEPN1-RM pattern, the most striking feature being the absence or severe atrophy of the semimembranosus muscle.[15]

Histopathologic phenotype

Multi-minicores were the most recurrent pathologic feature, present in 59.5% of biopsies and representing the main lesion in 49.4%, often associated with fiber size variation, type I fiber predominance and relative hypotrophy, internalized nuclei and mild dystrophic features, and notably mild increase in endomysial connective tissue (figure 5). In 6.3%, minicores were associated with eosinophilic inclusions compatible with Mallory-like bodies, exclusively found in quadriceps. Prominent dystrophic signs were present in 24.1%, either isolated or associated with minicores or "unspecific changes of internal structure" on oxidative stainings. A total of 25.3% of biopsies disclosed nonspecific myopathic findings, mainly fiber size variation, type I fiber predominance, or internalized nuclei. Rare rimmed vacuoles were found in 2 patients. Interestingly, patients having nonspecific biopsy abnormalities were younger than patients having more specific lesions (8.55 ± 5.3 vs 13.89 ± 11.7 years, 95% confidence interval 1.2–9.5, p = 0.012).

In 2 patients with biopsies from axial and limb muscles, axial muscles were more severely dystrophic or showed larger core lesions than limb muscles, consistently with clinical weakness distribution.

Long-term course and determinants of severity

Excepting one patient who died at 3 years of age, all acquired independent ambulation and improved motor performance during childhood. After implementation of efficient ventilation and arthrodesis in their teens, most patients remained stable for more than a decade. However, disease progressed steadily from the fourth decade of life (figure 2). Loss of ambulation occurred in 8 patients at ages 8–54 years (median 21.5, interquartile range 19.75), representing 10% of cases for whom follow-up information was available.

Scoliosis and restrictive respiratory failure were often diagnosed simultaneously around the end of the first decade. FVC was <39% in most patients and tended to decrease with age (figure 4, A and C). Analysis of a thoroughly documented subgroup of 11 patients demonstrated that scoliosis management had a major respiratory impact: spinal fusion led to a dramatic FVC drop in the immediate postoperative period, with return to preoperative or better values within 6 months in patients with intensive and regular postsurgical ventilation (figure 4F). Independently of interventions, we observed marked intraindividual variability in FVC values, with major fluctuations possibly due to fatigue or intercurrent infections (figure 4E).

The main predictive factor of vital prognosis was respiratory failure, with 50% of patients needing assisted ventilation within the first 13 years (figure 4D). Six patients died at ages 3, 5, 16, 58, and 59, due to respiratory failure (n = 2), sudden death (n = 2), choking (n = 1), or uncharacterized deterioration in a terminal patient (n = 1).

To assess potential disease progression determinants, we established the following arbitrary severity criteria: (1) prominent neonatal hypotonia or persistent lack of head control; (2) scoliosis or respiratory failure before age 10 years; (3) progressive motor disability causing loss of ambulation before adulthood. We identified 3 phenotypical groups (n = 81): severe (n = 23, 28.4%) when patients presented 2 or more criteria; moderate (n = 43, 53.1%) if only one criterion was present; and mild (n = 15, 18.5%) if none was fulfilled.

Patients with mild or moderate disease corresponded to the previously described classical form of the disease. In severe disease, earlier scoliosis and respiratory failure required assisted ventilation since early childhood. A subgroup of patients with a very severe phenotype showed ophthalmoparesia, rapidly progressive muscular weakness and respiratory failure, loss of ambulation before adulthood, and severe tetraparesis in the third decade of life. Strikingly, these patients with very severe disease showed from childhood subcutaneous adiposity with predominant abdominal distribution. Conversely, most patients with good motor abilities were extremely underweight. In 47 patients with anthropometrical data, we found a significant correlation between body weight and disease severity (p = 0.002). Weight gain often led to complaints of poorer functional performance and increased fatigue.

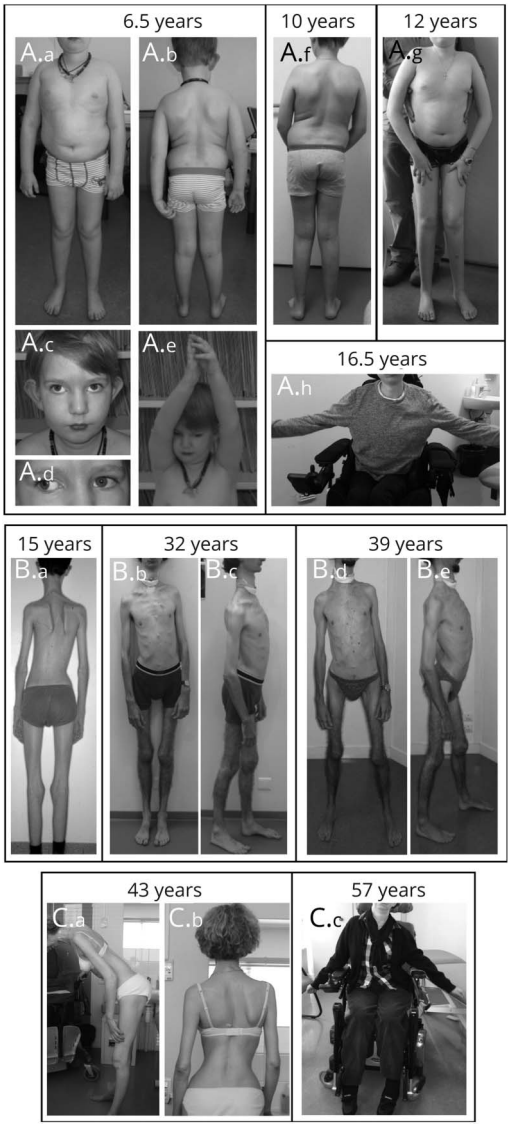
Aging was associated with significant progression even in patients with mild or moderate disease. This series includes 9 patients aged ≥35 years (35–58 years at last examination). Slow but steady increase of muscle weakness and fatigue from the fourth decade led to reduced gait perimeter and motor performances of upper and lower limbs (figure 2). Three patients with mild disease lost ambulation at ages 33, 38, and 54 years; others required a wheelchair for long distances. Swallowing difficulties were not uncommon in older patients and choking caused death in a 59-year-old patient. Another patient with mild disease developed severe tetraparesis, required PEG and ventilation more than 15 h/d, and died at 58 years of age due to general deterioration. The oldest patient is currently aged 55 years, remains ambulant, and leads an active professional life with nighttime ventilation, despite aggravation of his difficulties for climbing stairs or getting up from sitting from the end of the third decade. FVC in this age group was severely reduced but remained stable. However, because of progressive diaphragmatic weakness, patients became unable to lie supine.

Five adult patients carried pregnancies to term and gave birth by cesarean section. One reported worsening of motor abilities postpregnancy and another had eclampsia with acute pulmonary edema requiring a transient tracheostomy.

Clinical genetics

Transmission was autosomal recessive, without de novo mutations, all tested parents being healthy heterozygous carriers. Seventy-two patients were homozygous and 59 compound heterozygous.

Figure 2 Disease course in typical severe, moderate, and mild cases



(A) This severely affected patient presented with neonatal axial muscle weakness, required nighttime assisted ventilation since diagnosis at 6.5 years of age, and showed at that age sternocleidomastoid, deltoid, and leg amyotrophy (A.a and A.b), antigravity limb strength (A.e), and ophthalmoparesis with limited upward (A.c.) and horizontal (A.d.) eye movements. Note the typical *SEPN1*-related myopathy (SEPN1-RM) facial appearance (tubular nose, prominent nasal sella, low-set prominent ears and mild retrognathia, midsegment hypotrophy [A.c]), and increased trunk adiposity (A.a and A.b). He developed scoliosis from age 7 years (A.f), which eventually required arthrodesis, lost independent ambulation at 11 years (A.g), and was wheelchair-bound with severe limb weakness at 16 years (A.h, maximum antigravity power of upper limbs). (B) After spinal fusion and instauration of nocturnal ventilation through a tracheostomy at 15 years of age (B.a), this patient with moderate SEPN1-RM remained stable until the middle of the fourth decade (B.b and B.c), when progressive limb weakness led to a wider base of support, increased hyperlordosis (B.d and B.e), and limited upper limb abduction and ambulation. Note reduced anteroposterior thorax diameter, severe diffuse amyotrophy, and loss of subcutaneous fatty tissue. (C) One of the mildest cases in this series resulted in normal motor development including head control, rigid spine (C.a), and mild untreated scoliosis (C.b) and required assisted ventilation only after the age of 35 years. A myopathy was first suspected in the fourth decade due to progression of a previously mild muscle weakness. Continuous progression eventually led to loss of antigravity movements and ambulation and almost permanent ventilation by the age of 57 years (C.c, maximum upper limb abduction) and to death at age 58 years.

We found 65 variants (32 unreported) of the *SEPN1/SELENON* reference coding sequence (figure 6 and supplementary table 1, doi.org/10.5061/dryad.nzs7h44nj), including missense (n = 23, 35.4%), duplications/insertions (n = 14, 21.5%), deletions (n = 13, 20%), and nonsense mutations (n = 8, 12.3%); 29 variants predictedly produced truncated proteins (11 prone to nonsense-mediated decay [NMD]). Four variants leading to loss of the start codon, with subsequent translation and protein absence, were harbored by 29 patients (10 of them complete null). We also report the first *SEPN1* copy number variation (CNV) (c.[872+1_873-1][1602+1_1603-1]del), a large likely out-of-frame deletion affecting exons 7 to 12.

We found 6 intronic splicing variants and 1 homozygous single-point mutation in the *SEPN1* 3′ untranslated region SECIS (selenocysteine insertion sequence), an untranslated *cis* element necessary for selenocysteine integration. This modification abolishes the binding of SBP2, a central component of the selenocysteine insertion machinery, preventing UGA redefinition and leading to a premature stop codon.[17,18]

We observed clustering of mutations in exons 1, 6, 7, and 11 and no mutations in exon 3, spliced in the predominant human transcript.[19] The GC-rich exon 1, a remarkable hotspot, was the most frequently mutated (39.7% of patients) and harbored the highest number of variants (28% mutations). The most common variant, identified in 15 families of different origins, was a mutation of the starting codon (c.1A>G) that changes the initiator methionine codon to a valine codon, causing total loss of translation. We identified founder effects for the mutations c.817G>A (Iran and Turkey), c.943G>A (Northern Europe), and c.713dupA (Western Europe).

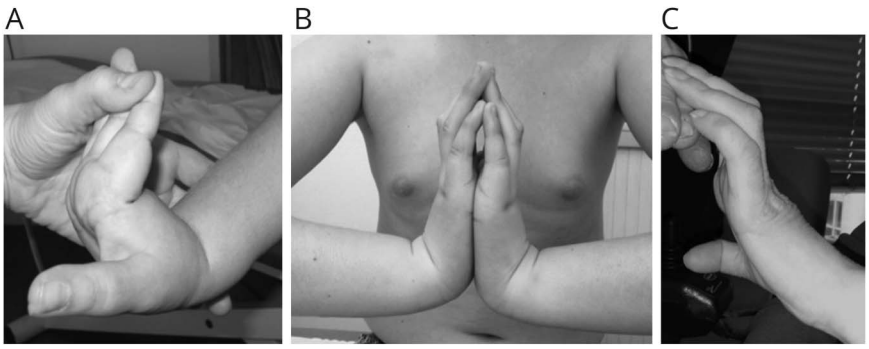
Genotype–phenotype correlations

Genotype–phenotype correlations, difficult to establish in a very rare disease due to low numbers of patients carrying the same mutation, were unknown for SEPN1-RM. This series revealed the first correlations between genetic defects and clinical severity, with no correlation between genotype and histopathologic findings.

Some exon 1 variants (c.1A>G, c.13_22dup and c.-19_73del) and the exon 6 c.818G>A mutation were most commonly found in patients with a severe phenotype, while other variants such as c.943G>A (exon7), c.1315C>T (exon 10), or c.1446delC (exon 11) were often found in milder cases.

Exon 1 homozygous mutations predicting total loss of translation (c.-19_73del and c.1A>G), carried by the patients with most severe disease in this series, were significantly associated with disease severity (p = 0.003). Moreover, homozygous or compound heterozygous patients carrying 2 variants located in any exon but predicting protein absence (by either loss of the start codon or NMD) exhibited more severe phenotypes (p = 0.017).

Figure 3 Hand hyperlaxity and finger flexor contractures



Moderate distal hyperlaxity was common in early childhood (A, 7-year-old patient) and often coexisted with finger flexor contractures visible upon wrist extension. The latter tended to appear from adolescence (B, 16-year-old patient) and became more prominent with age (C, 57-year-old patient).

Only missense mutations were present in the sequence encoding the selenoprotein N putative catalytic site (SCUG, exon 10).[20] They were identified in 23 patients (7 homozygous), most with moderate severity disease.

Discussion

This study reports the largest SEPN1-RM series and the first one including pediatric and older adult patients followed up for several decades, furthering our understanding of phenotypical spectrum and natural history. It also allows inferring information about SEPN1-RM prevalence. Our series includes 63 French patients, identified through the main reference laboratories performing *SELENON/SEPN1* screening as part of a national network. We also interrogated the other genetic diagnostic laboratories in France, which have identified 6 additional cases, thus very likely capturing virtually all the diagnosed patients in the country. A total number of 69 cases in France represents an estimated prevalence of 1.03 per million, consistent with a previous study of congenital muscular dystrophies in the United Kingdom.[21] This suggests that SEPN1-RM, although rare, is underrecognized. Several reasons might explain this, including the axial predominance of weakness, absence of biomarkers, histopathologic variability, and gene screen pitfalls.

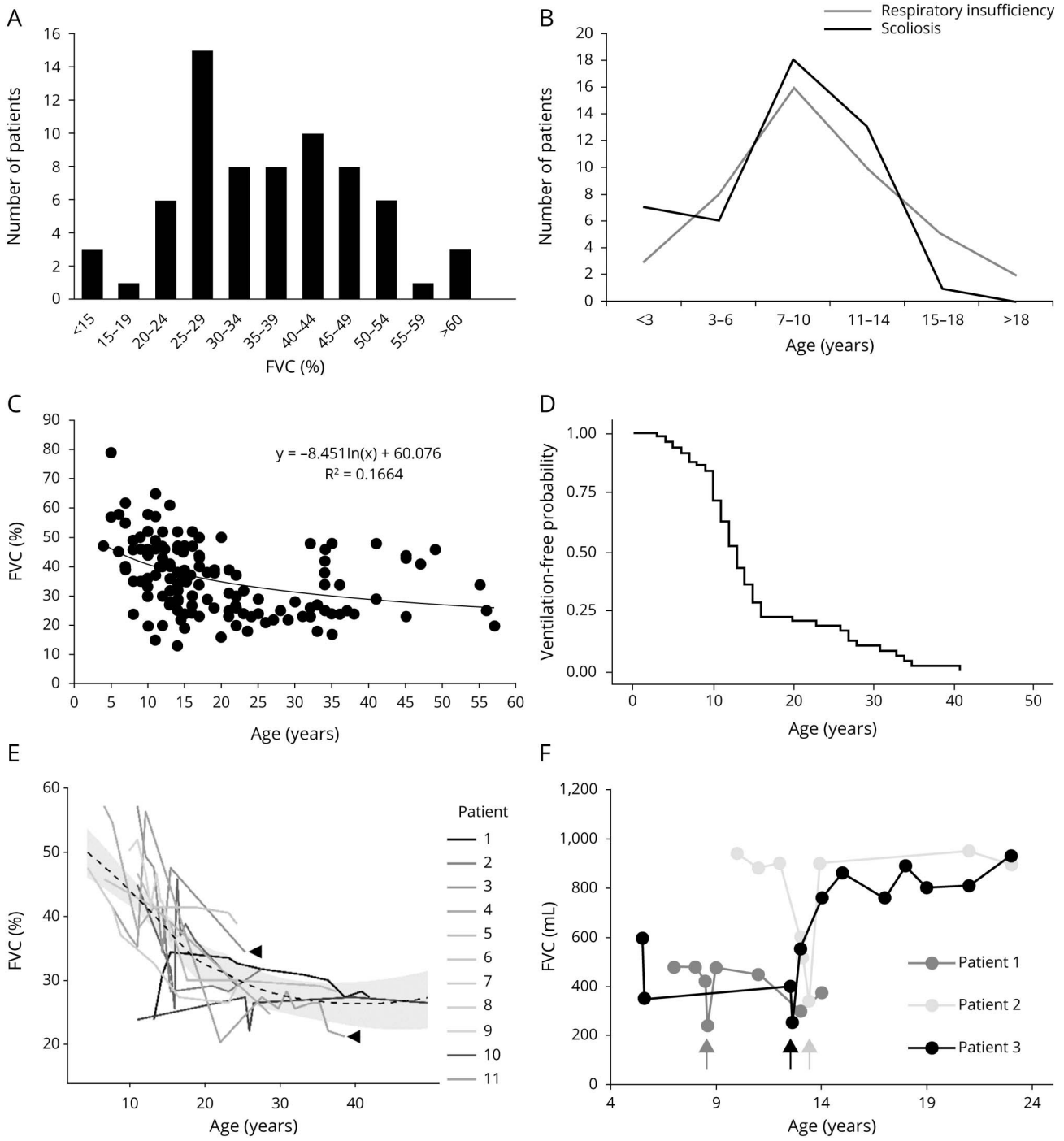
SEPN1-RM clinical features are homogeneous and distinctive and include a particular facial appearance, long slender neck, flat retracted thorax, severe axial weakness, and rigid spine. Indeed, axial muscles (and particularly the diaphragm) are known to be particularly vulnerable to oxidative stress, a known consequence of SEPN1 depletion.[12] Axial weakness and rigidity are generally present from an early age but often overlooked, since they are rarely a cause of spontaneous complaints and contrast with fairly preserved limb strength and ambulation. The suspicion of a muscle disorder is often hindered until the end of the first decade, when scoliosis and restrictive respiratory failure are detected. Interestingly, we show that ophthalmoparesis can be part of the SEPN1-RM phenotype and correlates with disease severity, which can be useful for differential diagnosis (i.e., with titinopathies). The scoliosis pattern and the predominantly cervicodorsal spinal rigidity in SEPN1-RM were also characteristic and different from the rigid spine in myopathies caused by mutations of *LMNA*,[22] *EMD*,[23] *FHL1*,[24] *COL6*,[25] *RYR1*,[26] *DNM2*,[27] *TTN*,[28,29] or *GAA*.[30,31] Finally, the homogeneous and recognizable radiologic pattern (axial muscle involvement, severe wasting of sternocleidomastoid muscles, and dramatic atrophy of semimembranosus, with relative preservation of the rectus femoris, long adductor, and gracilis)[15] can be useful for diagnosis even in very young patients or patients with mild disease.

This series confirms the unusually large SEPN1-RM histologic spectrum, and reveals some of its determinants. We found no correlation between the histopathologic presentation and clinical severity. Most biopsies were typical of a congenital myopathy, showing minicores, type 1 fiber predominance, and mild endomysial fibrosis. Moderate dystrophic features or protein aggregates were also found, although the latter typically affect a low percentage of fibers and were found only in quadriceps samples. We revealed a clear-cut discordance between severely dystrophic axial muscles and mildly myopathic limb muscles in the same patient. Thus, the site of biopsy can contribute to explain the histopathologic variability. Furthermore, younger ages correlated with less specific biopsy findings. Therefore, muscle biopsy might be best delayed until school age to increase the diagnostic yield, and could be reserved for cases without a typical phenotype or when other tests have been inconclusive.

Along these lines, exon 1 emerged as a major hotspot for *SEPN1* mutations and is poorly or not covered by NGS panels, probably contributing to underdiagnosis. Our findings confirm that clinical recognition of the SEPN1-RM phenotype is essential and sufficient in most patients for indicating *SEPN1* genetic testing, which should systematically include Sanger sequencing of exon 1. Moreover, identification of the first *SEPN1* CNV highlights the need to search for large genomic rearrangements, particularly when only one *SEPN1* pathogenic variant has been detected.

On another note, most *SEPN1* mutations predicted loss of function, indicating that SEPN1-KO models are relevant for

Figure 4 Respiratory involvement

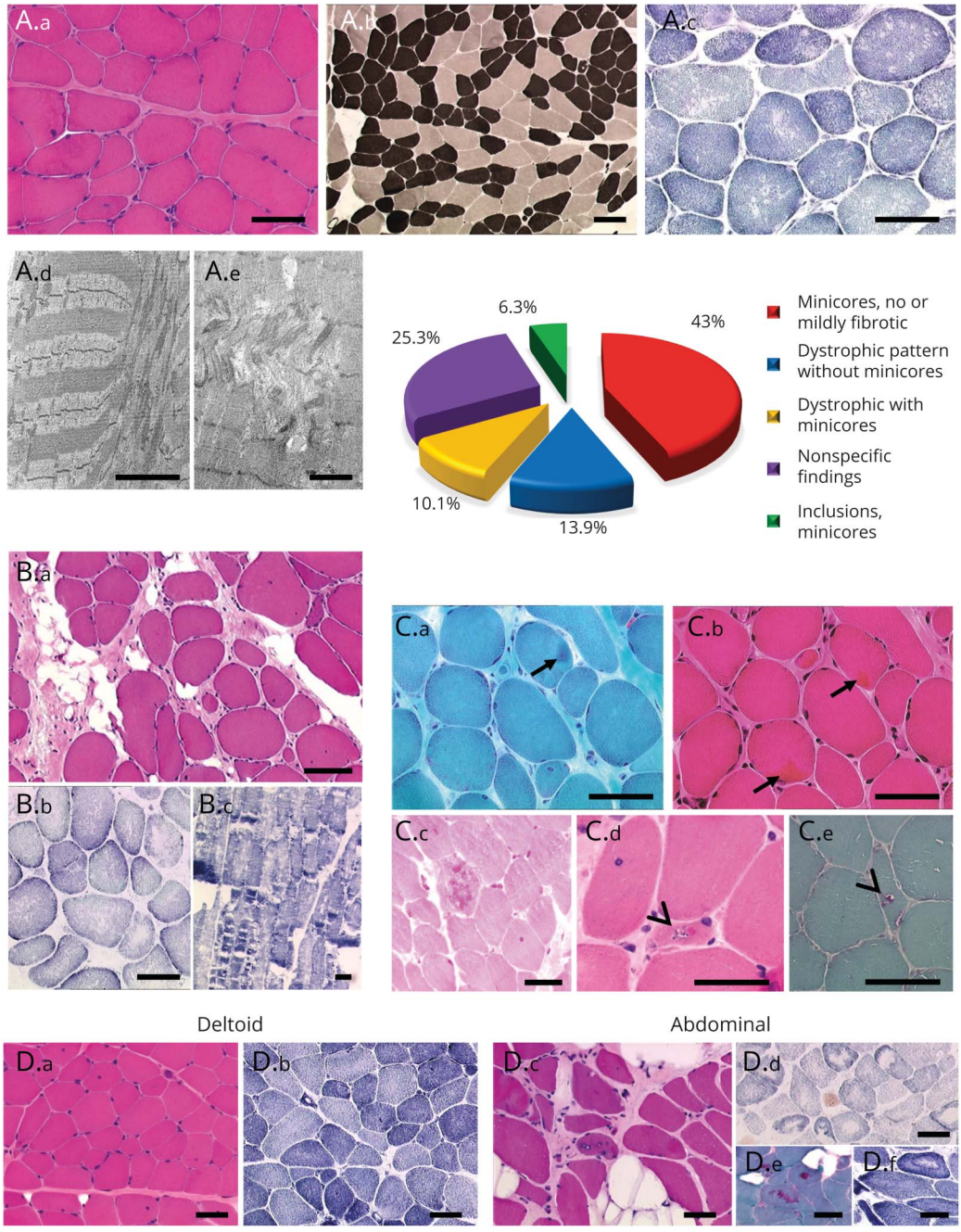


(A) Distribution of forced vital capacity (FVC) (% of predicted values) in 69 cases shows that most patients had FVC <39%, the most frequent range being between 25% and 29%. (B) Respiratory insufficiency (gray line) or scoliosis (black line) were first detected in most patients around the same age, most commonly between 7 and 10 years. (C) Progression of FVC in 32 patients (ages 4–58 years) revealed decrease of FVC with age in years using a logarithmic regression (R^2 = 0.16642). Individual values are shown as black dots. (D) Kaplan-Meier curve showing ventilation-free probability with age. (E) Progression of respiratory involvement in 11 patients, revealing extreme variability between patients with similar disease severity. Note also intrapatient variability in FVC values (arrowheads). (F) Follow-up of respiratory involvement before and after surgical correction of scoliosis in 3 patients. FVC typically dropped in the postsurgical period (arrows) and then came back to previous or even higher values with correct postoperative management including ventilation.

SEPN1-RM studies. Interestingly, all pathogenic variants located around or in the sequence encoding the potential catalytic site (exon 10) were missense changes. The EF-hand domain-encoding sequence showed no mutation.

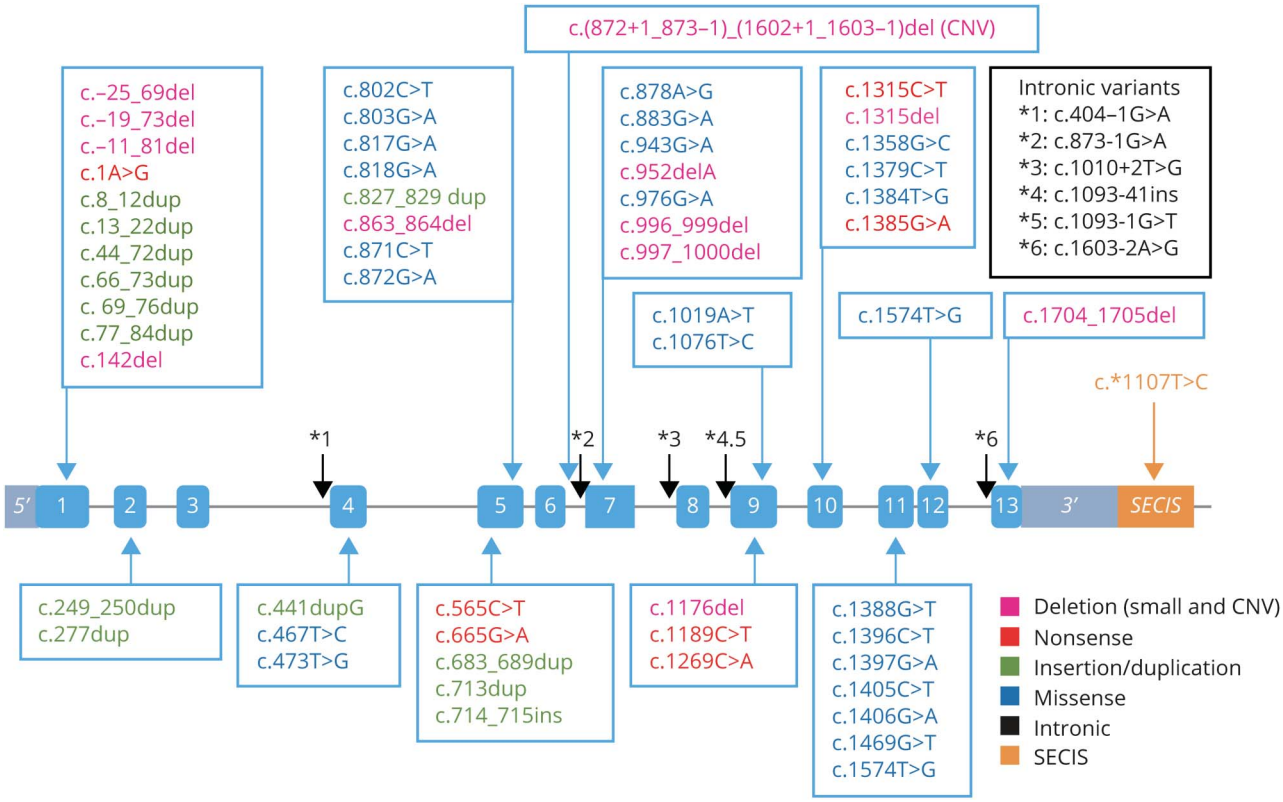
This study reveals SEPN1-RM as a more severe and progressive disease than previously thought. While motor abilities were reported to be stable, we found loss of ambulation in 10% of the cases with full follow-up data. Muscle functional performance

Figure 5 Histopathologic patterns and different histologic severity in axial vs limb muscles



The relative frequency of the different histopathologic patterns observed in this series (n = 78) is represented in the graph. Foci of sarcomere disorganization and mitochondria depletion, spanning only a few sarcomeres on the longitudinal axis of the fiber (minicores), were observed in 60% of the biopsies (A.c–A.e and B.b and B.c). (A) The most common pattern was typical of a congenital myopathy with minicores (multi-minicore disease), including mild or no endomysial fibrosis (A.a), type I fiber predominance and relative hypotrophy (dark fibers, A.b), and multiple lighter zones devoid of succinate dehydrogenase (SDH) or nicotinamide adenine dinucleotide (NADH) enzymatic activity (A.c) corresponding to mitochondria depletion and sarcomere disorganization on electron microscopy (EM) (minicores) (A.d and A.e). (B) Around 24% of biopsies showed a mild to moderate congenital muscular dystrophy pattern, associated with either abundant or scattered/inconspicuous minicores. Note prominent endomysial fibroadiposis but rare necrotic or regenerating fibers (B.a). (C) Eosinophilic inclusions compatible with Mallory body–like inclusions (arrows, C.a and C.b) or rimmed vacuoles (arrowheads, C.d and C.e) were identified in some samples but typically involved a small percentage of fibers. Thus they were easily overlooked unless specifically searched for. (D) Two muscle samples taken from the same patient at 12 years of age revealed that histopathologic changes were more severe in axial than in limb muscles, mirroring the clinical situation. Her deltoid muscle (D.a and D.b) showed minor myopathic changes, with mild fiber size variation and scattered internalized nuclei and minicores. In contrast, her abdominal muscles revealed major dystrophic changes with muscle fiber loss, fatty-adipose replacement, rimmed vacuoles (D.c), rod-like inclusions (D.e), multi-minicores (D.d), and also well-delimited cores with a hyperoxidative perilesional rim (similar to those observed in central core disease) (D.f). Transversal frozen sections stained with hematoxylin & eosin (A.a, B.a, C.b–C.d, D.a and D.c), reduced NADH (A.c, B.c, D.b and D.f), ATPase 4.6 (A.b), SDH (B.b and D.d), modified Gomori trichrome (C.a and C.e, D.e); longitudinal EM sections (A.d and A.e). Scale bars: 50 μm except for A.d and A.e: 2 μm.

Figure 6 Schematic representation of the *SEPN1* (SELENON) gene and localization of the identified mutations



Exons are depicted in light blue and the 3′ untranslated region (UTR) SECIS element in orange. The putative reductase domain containing the only selenocysteine residue in SEPN1 is encoded by exon 10. The EF-hand domain, potentially calcium-binding, is encoded by exon 2. Color code for variants: pink, deletion; green, insertions/duplications; blue, missense; red, nonsense; black, intronic variants affecting splicing; orange, variants affecting SEPN1 3′ UTR SECIS element. CNV = copy number variation; SECIS = selenocysteine insertion sequence.

and respiratory function (particularly diaphragmatic fatigue) declined systematically from the end of the third decade, even in mild cases. Mortality at young age was observed in 3 severe patients and in 18 relatives, most of them never ventilated. But lifespan was reduced even in 2 mild cases with optimum respiratory support, the eldest patient being currently 55 years old.

Management of the scoliosis and respiratory failure was a key determinant of prognosis. We previously reported that early noninvasive ventilation may initially stabilize the decline in respiratory muscle strength.[32] Our current data also reveal that scoliosis surgery had a positive impact on the respiratory function but induced a major drop in FVC in the immediate postsurgical period. Intensive or permanent ventilation at this decisive time was critical to restore or improve FVC presurgery values.

Other factors associated with disease severity were the type of *SELENON*/*SEPN1* gene defects and previously unreported body mass abnormalities. Indeed, the analysis of this series allowed us to establish the first phenotype–genotype correlations in SEPN1-RM. Some exon 1 variants were commonly found in patients with a severe phenotype, although the small number of patients harboring each individual variant and the different associated mutations in trans precluded statistical significance. However, biallelic null mutations significantly correlated with higher disease severity.

We also found a significant correlation between body weight and disease severity. We identified a subgroup of patients with increased adiposity since childhood who showed rapid disease progression leading to severe weakness (including non-weight-bearing and extraocular muscles) and loss of ambulation before adulthood. This extramuscular phenotype is different from secondary weight gain in a wheelchair-bound patient and could be related to SEPN1-RM pathophysiologic mechanisms involving defective mitochondrial bioenergetics and lipid metabolism in muscle.[10,12,33,34,37] Indeed, we reported that SEPN1 depletion increases susceptibility to insulin resistance and higher toxicity of saturated fatty acids, which triggers chronic endoplasmic reticulum stress and weakness in skeletal muscle in SEPN1-RM models.[5,33] Thus, high calorie intake, particularly from a high-fat diet, could trigger or aggravate glucose metabolism abnormalities, oxidative/endoplasmic reticulum stress, and muscle weakness. Consequently, systematic administration of hypercaloric diets/supplements might not be indicated on the basis of low weight alone, unless there are other clear markers of malnutrition.

Our results have significant implications for the identification of outcomes, a keystone for clinical trials. In recent years, significant progress has been achieved in the identification of SEPN1-RM pathophysiologic pathways targetable with existing drugs.[10,12,33,34] The antioxidant N-acetylcysteine has been identified as an effective treatment ex vivo, which led to a small pilot trial (ClinicalTrials.gov identifier: NCT02505087) whose results are pending. Multicentric, international phase II–III trials require overcoming bottlenecks that are highlighted here. One is the predominantly axial weakness, since there are few validated measures of axial muscle power. We also found important intrapatient variability in FVC, potentially explained by fatigability of the diaphragm and respiratory muscles, suggesting that FVC is not fully reliable as an outcome measure. Other respiratory function parameters, including pressure values, should be included in future prospective studies. Another variability factor is heterogeneous orthopedic and respiratory management, particularly around spinal surgery, which has a major functional impact. This together with slow progression until the fourth decade hinders the choice of outcome measures to evaluate treatment efficacy. We propose straightforward disease severity criteria, thus defining more homogeneous groups, and provide Kaplan-Meier curves quantifying ventilation-free probability to evaluate impact of potential treatments. We also suggest that age stratification could be useful, since limb strength is stable or slowly progressive in younger patients but steadily progressive after the fourth decade.

Homogeneous management recommendations would reduce variability and improve vital prognosis. Based on our data, we recommend systematic sleep studies even in young children or in the absence of daytime signs of respiratory failure or major FVC decrease. Noninvasive ventilation should be initiated as soon as respiratory failure or nocturnal hypoventilation are detected, adjusted regularly,[35,36] and sustained/intensified postarthrodesis. Follow-up should include yearly respiratory and cardiac evaluations, given the possibility of pulmonary hypertension or secondary right-ventricle failure. We also recommend yearly spine surveillance, which can be intensified to every 6 months around the rapid growth spurt in adolescence due to the probability of rapid evolution. Finally, we suggest performing oral glucose tolerance test, particularly in adolescents and adults, and tailoring BMI control to SEPN1-RM particularities.

This work improves our understanding of SEPN1-RM phenotype and natural history in children and adults. It will hopefully inform clinical practice, contributing to improve diagnosis, management, and follow-up and to increase disease awareness and recognition of its phenotypic specificities. Our results also pave the way for the design of prospective natural history studies and clinical trials in the near future.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix 1 *(continued)*

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Continued

Appendix 1 *(continued)*

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References

1. Moghadaszadeh B, Desguerre I, Topaloglu H, et al. Identification of a new locus for a peculiar form of congenital muscular dystrophy with early rigidity of the spine, on chromosome 1p35-36. Am J Hum Genet 1998;62:1439–1445.
2. Lescure A, Gautheret D, Carbon P, Krol A. Novel selenoproteins identified in silico and in vivo by using a conserved RNA structural motif. J Biol Chem 1999;274:38147–38154.
3. Moghadaszadeh B, Petit N, Jaillard C, et al. Mutations in SEPN1 cause congenital muscular dystrophy with spinal rigidity and restrictive respiratory syndrome. Nat Genet 2001;29:17–18.
4. Ferreiro A, Quijano-Roy S, Pichereau C, et al. Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multiminicore disease: reassessing the nosology of early-onset myopathies. Am J Hum Genet 2002;71:739–749.
5. Clarke NF, Kidson W, Quijano-Roy S, et al. SEPN1: associated with congenital fiber-type disproportion and insulin resistance. Ann Neurol 2006;59:546–552.
6. Ferreiro A, Ceuterick-de Groote C, Marks JJ, et al. Desmin-related myopathy with Mallory body-like inclusions is caused by mutations of the selenoprotein N gene. Ann Neurol 2004;55:676–686.
7. Scoto M, Cirak S, Mein R, et al. SEPN1-related myopathies: clinical course in a large cohort of patients. Neurology 2011;76:2073–2078.
8. Ardissone A, Bragato C, Blasevich F, et al. SEPN1-related myopathy in three patients: novel mutations and diagnostic clues. Eur J Pediatr 2016;175:1113–1118.
9. Schara U, Kress W, Bönnemann CG, et al. The phenotype and long-term follow-up in 11 patients with juvenile selenoprotein N1-related myopathy. Eur J Paediatr Neurol 2008;12:224–230.
10. Arbogast S, Ferreiro A. Selenoproteins and protection against oxidative stress: selenoprotein N as a novel player at the crossroads of redox signaling and calcium homeostasis. Antioxid Redox Signal 2010;12:893–904.
11. Marino M, Stoilova T, Giorgi C, et al. SEPN1, an endoplasmic reticulum-localized selenoprotein linked to skeletal muscle pathology, counteracts hyperoxidation by means of redox-regulating SERCA2 pump activity. Hum Mol Genet 2015;24:1843–1855.
12. Arbogast S, Beuvin M, Fraysse B, Zhou H, Muntoni F, Ferreiro A. Oxidative stress in SEPN1-related myopathy: from pathophysiology to treatment. Ann Neurol 2009;65:677–686.
13. Moulin M, Ferreiro A. Muscle redox disturbances and oxidative stress as pathomechanisms and therapeutic targets in early-onset myopathies. Semin Cell Dev Biol 2017;64:213–223.
14. Rederstorff M, Castets P, Arbogast S, et al. Increased muscle stress-sensitivity induced by selenoprotein N inactivation in mouse: a mammalian model for SEPN1-related myopathy. PLoS One 2011;6:e23094.
15. Hankiewicz K, Carlier RY, Lazaro L, et al. Whole-body muscle magnetic resonance imaging in SEPN1-related myopathy shows a homogeneous and recognizable pattern. Muscle Nerve 2015;52:728–735.
16. Nigro V, Piluso G. Next generation sequencing (NGS) strategies for the genetic testing of myopathies. Acta Myol 2012;31:196–200.

17. Lescure A, Rederstorff M, Krol A, Guicheney P, Allamand V. Selenoprotein function and muscle disease. Biochim Biophys Acta 2009;1790:1569–1574.
18. Maiti B, Arbogast S, Allamand V, et al. A mutation in the *SEPN1* selenocysteine redefinition element (SRE) reduces selenocysteine incorporation and leads to *SEPN1*-related myopathy. Hum Mutat 2009;30:411–416.
19. Petit N, Lescure A, Rederstorff M, et al. Selenoprotein N: an endoplasmic reticulum glycoprotein with an early developmental expression pattern. Hum Mol Genet 2003;12:1045–1053.
20. Castets P, Lescure A, Guicheney P, Allamand V. Selenoprotein N in skeletal muscle: from diseases to function. J Mol Med 2012;90:1095–1107.
21. Sframeli M, Sarkozy A, Bertoli M, et al. Congenital muscular dystrophies in the UK population: clinical and molecular spectrum of a large cohort diagnosed over a 12-year period. Neuromuscul Disord 2017;27:793–803.
22. Quijano-Roy S, Mbieleu B, Bönnemann CG, et al. De novo *LMNA* mutations cause a new form of congenital muscular dystrophy. Ann Neurol 2008;64:177–186.
23. Kubo S, Tsukahara T, Takemitsu M, et al. Presence of emerinopathy in cases of rigid spine syndrome. Neuromuscul Disord 1998;8:502–507.
24. Shalaby S, Hayashi YK, Goto K, et al. Rigid spine syndrome caused by a novel mutation in four-and-a-half LIM domain 1 gene (FHL1). Neuromuscul Disord 2008;18:959–961.
25. Bönnemann CG. The collagen VI-related myopathies. Handb Clin Neurol 2011:81–96.
26. Bharucha-Goebel DX, Santi M, Medne L, et al. Severe congenital RYR1-associated myopathy: the expanding clinicopathologic and genetic spectrum. Neurology 2013;80:1584–1589.
27. Quijano-Roy S, Avila-Smirnow D, Carlier RY; WB-MRI muscle study group. Whole body muscle MRI protocol: pattern recognition in early onset NM disorders. Neuromuscul Disord 2012;22(suppl 2):S68–S84.
28. Oates EC, Jones KJ, Donkervoort S, et al. Congenital titinopathy: comprehensive characterization and pathogenic insights. Ann Neurol 2018;83:1105–1124.
29. Chauveau C, Bonnemann CG, Julien C, et al. Recessive TTN truncating mutations define novel forms of core myopathy with heart disease. Hum Mol Genet 2014;23:980–991.
30. Fadic R, Waclawik AJ, Brooks BR, Lotz BP. The rigid spine syndrome due to acid maltase deficiency. Muscle Nerve 1997;20:364–366.
31. Laforêt P, Doppler V, Caillaud C, et al. Rigid spine syndrome revealing late-onset Pompe disease. Neuromuscul Disord 2010;20:128–130.
32. Caggiano S, Khirani S, Dabaj I, et al. Diaphragmatic dysfunction in SEPN1-related myopathy. Neuromuscul Disord 2017;27:747–755.
33. Varone E, Pozzer D, Di Modica S, et al. SELENON (SEPN1) protects skeletal muscle from saturated fatty acid-induced ER stress and insulin resistance. Redox Biol 2019;24:101176.
34. Pozzer D, Varone E, Chernorudskiy A, et al. A maladaptive ER stress response triggers dysfunction in highly active muscles of mice with SELENON loss. Redox Biol 2019;20:354–366.
35. Wallgren-Pettersson C, Bushby K, Mellies U, Simonds A; ENMC. 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders: congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II) 4-6 April 2003, Naarden, the Netherlands. Neuromuscul Disord 2004;14:56–69.
36. Wang CH, Bonnemann CG, Rutkowski A, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol 2010;25:1559–1581.
37. Filipe A, Chernorudskiy A, Arbogast S, et al. Defective endoplasmic reticulum-mitochondria contacts and bioenergetics in SEPN1-related myopathy. Cell Death Differ Epub 2020 Jul 13.