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Spinal muscular atrophy with respiratory distress type 1: A multicenter retrospective study

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Abstract

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare autosomal recessive neuromuscular disorder characterized by progressive motor and respiratory decline during the first year of life. Early and late-onset cases have recently been reported, although not meeting the established diagnostic criteria, these cases have been genotyped. We thus conducted a national multicenter observational retrospective study to determine the prognosis of children with SMARD1 according to their phenotype. We recorded all known French pediatric cases with mutations identified on the *immunoglobulin μ-binding protein 2* gene and the presence of respiratory symptoms. Thirty centers provided 22 observations. A diaphragmatic palsy was diagnosed 1.5 months ($p = 0.02$) after first respiratory symptoms, and hypotonia preceded areflexia by 4 months ($p = 0.02$). Early onset of symptoms leading to specialist consultation before the age of 3 months was associated with a significantly worse prognosis ($p < 0.01$). Among the 6 patients who were still alive, all were tracheostomized. Only one case survived beyond 2 years without artificial ventilation. The remaining patients died at a median age of 7 months. Our results may help pediatricians to provide medical information to parents and improve the decision-making process of setting up life support.

Keywords: SMARD1; DSMA1; Multicenter; Prognosis; IGHMBP2; Heterogeneity.

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1. Introduction

Spinal muscular atrophy with respiratory distress (SMARD) is an autosomal recessive neuromuscular disorder historically described as a variant of spinal muscular atrophy (SMA) [1]; although SMARD remains less well known, it is more severe. The prevalence has not yet been determined, and the phenotype might be heterogeneous [2–4].

In 1974, Mellins et al. [1] were the first to describe 2 unusual cases of infants with SMA who presented acute respiratory failure with bilateral diaphragmatic palsy and later developed global weakness with areflexia. A distinct phenotype was gradually described [5–8]: hypotonia with a rather distal sensorimotor neuropathy and amyotrophy [9].

As this disorder seemed genetically different [10], Grohmann et al. in 1999 [11] launched a whole genome scan in a consanguineous family, which revealed homozygous markers at the 11q13-q21 locus, defining what is now known as SMARD1. The disease is also currently known as distal spinal muscular atrophy 1 (DSMA1, MIM#604320) and distal hereditary motor neuropathy type VI (dHMN6) [2]. The study of a transgenic model, the neuromuscular degeneration (nmd) mouse, demonstrated [12] that this locus encodes for the immunoglobulin μ-binding protein 2 (IGHMBP2, also called SMUBP2 [13]). Since then, dozens of mutations have been described, most of them point mutations [14], but no genotype-phenotype correlation has thus far been conclusively proved [2,3].

The IGHMBP2 protein is composed of 993 amino acids [15] and belongs to the group of ATP-dependent $5'\rightarrow3'$ helicases [16]. It is composed of three domains: DEAD box-like (i.e., the amino acids D-E-A-D or Asp-Glu-Ala-Asp), zinc finger, and R3H (which contains 1 Arg and 1 His). [17] The lack of a functional helicase, and thus the lack of mRNA maturation in motoneurons, could lead to the symptomatology. However, mutations sparing the helicase domain have also been described and might involve the R3H domain instead [17]. Likewise, why motoneurons are specifically harmed remains unsolved, particularly since IGHMBP2 synthesis is said to be ubiquitous [3]. There are indeed still many unanswered questions about the origins of SMARD1.

Once the causal gene had been identified, Grohmann et al. [18] reviewed 29 genotyped SMARD1 cases and described such early symptoms as intrauterine growth retardation (IUGR), weak cry, and distal deformities (equinovarus feet and fatty finger pads [18–20]). They also reported a symptom-free interval that varied between 1 and 6 months before the first onset of respiratory and/or neurological symptoms, and a sensory and autonomic neuropathy [9,20–22]. In the same year, Pitt et al. [23] proposed clinical criteria based on the phenotypic data from 13 cases (listed in Table 1).

Guenther et al. [14] then presented a mathematical algorithm that predicted the existence of *IGHMBP2* mutations with 98% sensitivity and 92% specificity in 141 patients with respiratory distress and an SMA phenotype: “manifestation of respiratory failure between 6 weeks and 6 months” AND “presence of diaphragmatic eventration” OR “preterm birth.”

Table 1
SMARD1 diagnostic criteria from Pitt et al. [23].

Clinical criteria	Histopathological criteria	EMG[2] criteria
(i) Low birth weight below the 3rd centile; (ii) Onset of symptoms within the first 3 months; (iii) Diaphragmatic weakness either unilaterally or bilaterally; (iv) Ventilator dependence within less than one month of onset with an inability to wean; and (v) Absence of other dysmorphology or other conditions.	(i) A shift to the left of myelinated fiber size in sural nerve biopsies[1]; (ii) Minimal evidence of ongoing myelinated fiber degeneration in biopsies taken up to 3 ± 4 months; and (iii) No evidence of regeneration or demyelination, which might account for the change in fiber size.	(i) Evidence of distal denervation, acute or chronic; (ii) Evidence of severe s lowing (< 70% of LLN[3]) in one or more nerves (motor or sensory).

[1] Since myelin sheath thickness was found to be appropriate for axon size, the fiber size change must have originated from the axon.
[2] EMG: electromyography.
[3] LLN: lower limit of normal range.

The literature suggests the course is severe and unremitting, as an overwhelming majority will die from respiratory failure before reaching 13 months of age unless they are put on permanent mechanical ventilation [3]. Only a few manage to reach adulthood [24,25]. Mild phenotypes [4,26–29] and severe early-onset phenotypes [6,22,30] have been observed, without specific genetic features. Moreover, these atypical clinical presentations are neglected in the diagnostic criteria by Pitt and/or Guenther. The most striking example is the 2 siblings carrying the same mutation who followed markedly contrasting clinical courses: the first died of sudden respiratory failure at 6 months and the second showed a mild sleep hypoventilation at 12 years [31].

A more thorough knowledge of the natural history of SMARD1 is thus required for the ongoing development of innovative therapeutics. Since the phenotype is heterogeneous, we assume predictive factors might exist. Therefore, the main purpose of this study was to conduct a retrospective national survival analysis of SMARD1 patients, with the secondary aim being to deduce the prognostic factors by analyzing the phenotypic spectrum.

2. Patients and methods

2.1. Patients

We performed a national observational retrospective study.

Children included were those who had been diagnosed with a homozygous or compound heterozygous *IGHMBP2* mutation since 2000 (date of the first onset of this genetic

Table 2
Semiquantitative original scoring system, from Eckart et al. [3].

1	Onset of mechanical ventilation
2	Onset of muscle weakness
3	Remaining antigravity movements in arms
4	Remaining antigravity movements in legs
5	Sitting without support
6	Holding the head upright while in sitting position
7	Reduction in facial expression
8	Ability to speak
9	Freedom from cerebral seizures
10	Dysfunction of the autonomic nervous system

testing in France) and who had presented the first respiratory symptoms before the age of 18 years. Patients were detected from all French genetics laboratories accredited for sequencing the *IGHMBP2* gene between 2000 and 2017 (Necker's, Bron's, Strasbourg's and Limoges' genetic laboratory), and information collected from health facilities which followed them and/or requested this genetic testing: French university hospitals, French Reference Centers for neuromuscular diseases and rare peripheral neuropathies, and Competence Centers for neurological diseases [32]. Thus, a total of 42 medical practitioners (21 pediatric neurologists, 20 geneticists and 1 pediatric intensive care physician) were contacted. Clinical, genetic and histopathological data were collected from medical records by the referring clinician and recorded on a standardized and anonymized case report form. Data collection took place between January and March 2017.

2.2. Study endpoints

The primary study endpoint was life span, and all other criteria were considered as secondary.

2.2.1. Clinical items

Data were collected on familial history of SMARD1 or sudden infant death syndrome [18], pregnancy, and the child's condition at birth and during the neonatal period.

Extensive information was collected during the first examination by a neuropediatrician or pediatric intensivist; this included the patient's age, the reasons for consultation and the outcome of the physical examination at that time from neurological, respiratory, nutritional and orthopedic perspectives. Early disease onset was defined by the onset of symptoms of respiratory distress or muscular weakness before 3 months of age. The cut-off was based on the 2012 results of Eckart et al. [3]: the clinical condition at 3 months was significantly correlated with the clinical outcome at 1 and 4 years old; this had no biological significance but was easy to use in clinical practice.

Regarding neurological assessment, the motor development milestones and communication skills were recorded, notably those specified in the semi-quantitative scoring system of Eckart et al. [3] (Table 2), including possible losses.

In addition, the Brooke scale [33] and the Vignos scale [34] were used to evaluate upper and lower body motor function. They were scored in line with the recommendations of the French National Authority for Health concerning neuromuscular disorders (2001) [35]. The higher the score, the more severe the decrement in function was.

We also recorded whether muscle wasting was distal or proximal, affecting the upper or the lower limbs, and whether there were signs of central nervous system damage. Respiratory items were recorded (age of onset, occurrence of bronchial congestion, the need for respiratory assistance or comfort care), as were the gastrointestinal features (the need for enteral feeding through a nasogastric tube or gastrostomy) and orthopedic symptomatology.

Regarding growth monitoring, weight in kilograms and length and head circumference in centimeters were collected at birth and at the first and most recent examinations by a specialist. The measures were then converted to percentiles using the World Health Organization Set 2 Growth Charts [36]. For premature infants (born before 37 weeks of gestation), we instead used Babson and Bend's chart [37] until they reached 10 weeks post-term, after which we used the World Health Organization Growth Charts using the corrected postnatal age until 24 months old.

Last, we recorded hospital admissions and lengths of stay over the course of the disease, and for the children who had died by the end of the study we reported the date of death and whether a multidisciplinary palliative care meeting had been held beforehand.

2.2.2. Paraclinical investigations

The discovery of phrenic palsy, whether unilateral or bilateral, was further explored and diagnosed by chest X-ray or fluoroscopy. In order to simplify the interpretation, phrenic palsy results will be shown alongside the respiratory items in the clinical results.

Molecular diagnosis of SMARD1 was based on the detection of *IGHMBP2* mutations after the coding regions and flanking introns were sequenced with the Sanger method using either the ABI3100 (Necker's genetic laboratory) or the ABIPRISM3130×1/3730 (Bron's laboratory) Genetic Analyzer from Applied Biosystems®. Variant pathogenicity was analyzed with Alamut® Visual v2.7rev.1 software (Interactive Biosoftware, 2015) with reference to the latest human genomic assembly submitted by the Genome Reference Consortium: GRC Human Build 38 to the GenBank database [38]. *IGHMBP2*'s mRNA is referred to as NM_002180.2 according to the National Center for Biotechnology Information Reference Sequence Database [39]. Each mutation was labeled as "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," or "benign" according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines. [40] Variants were represented in line with the recommendations of the Human Genome Variation Society [41]. However, when Sanger sequencing revealed no point mutation whereas clinical suspicion of SMARD1 remained strong, other options were considered, including mRNA sequencing with multiplex ligation-dependent probe amplification sequencing (MRC Holland Kit, version

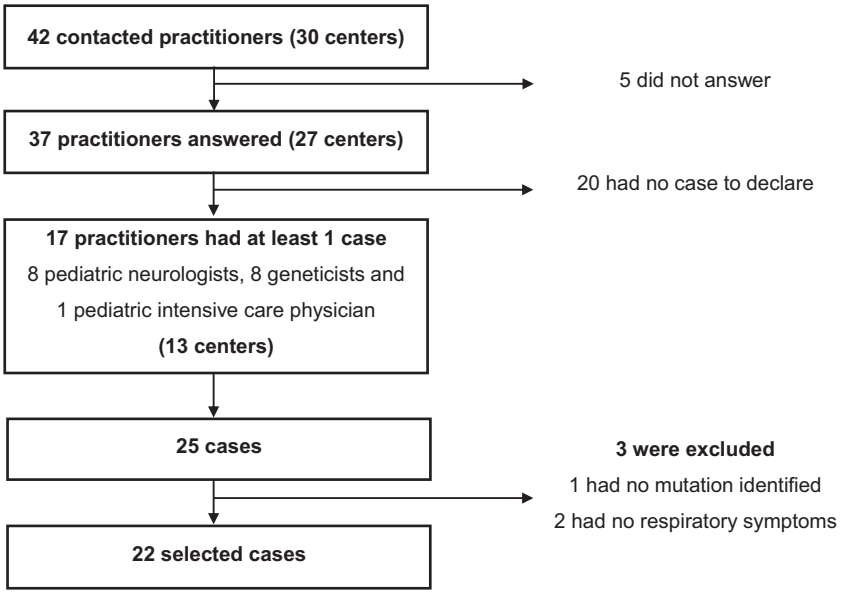

Fig. 1. Flow chart.

P058-A1-IGHMBP2), next generation sequencing (NGS): a panel for "neuropathy" (performed by the genetics laboratory of Limoges), or exome analysis (Ion AmpliSeq Exome RDY Kit ref 44898380). All the new variants were submitted to ClinVar database. [42]

A retrospective analysis of the data from nerve conduction studies (NCS) and needle electromyography (EMG) was performed. The data were analyzed according to age-adjusted normative data from the literature [43].

Nerve, muscle and skin biopsies were fixed, paraffin-embedded, and then cut with a microtome into thin sections and examined under an electron microscope. Samples were analyzed with an optical microscope and depicted by the local pathologist, sometimes after histoenzymology and immunohistochemical study.

Creatine kinase (CK) levels, liver function tests and abnormal metabolic balance results were collected.

2.3. Statistical analysis

Quantitative variables were expressed as means ± standard deviations (in brackets) or medians with interquartile range (IQR), and qualitative variables as percentages. Chi squared tests or Fisher exact tests were used to compare categorical variables, and *t*-tests or non-parametric Wilcoxon tests were used for continuous variables. Overall survival was defined as the time from birth to death or was censored at the date last known alive and analyzed using the Kaplan-Meier method. A log-rank test was used to compare survival between the patient subgroups (with or without a ventilator support, nonsense mutation, preterm birth, IUGR under the 10th percentile and according to the age at first examination, symptom onset, allelic status).

Tests were two-sided and p values lower than 0.05 were considered significant. Data analysis was performed using Stata 14.2 software (Stata Corporation, College Station, TX).

2.4. Ethics

This work was supported by a local non-profit association promoting the development of pediatric neurology and neuropsychology (Association AT3C). The authors have no conflict of interest to declare.

Since neither distinctive information nor patient images were recorded and the study was observational and retrospective, this research did not require ethics approval according to French laws. The National Commission on Informatics and Liberty, the national committee for data privacy, gave approval (decision number 1976742).

3. Results

3.1. Patients

Twenty-two children with SMARD1 born between 2000 and 2015 were identified, 15 of whom were male (68.2%). Median age at first consultation was 3.3 months [IQR: 1.7–5.5]. Three cases of this series have already been published [19,22,44].

A detailed flow chart is represented below in Fig. 1.

3.2. Antenatal and perinatal data

Two children were siblings. There was no other family history of SMARD1, and only one case of sudden infant death syndrome was notified. Parental consanguinity was present in 38.1% of the families. During the antenatal period, 50% of the children were diagnosed with IUGR and 2 cases of decreased fetal movements and 3 cases of amniotic fluid abnormality were reported.

The median gestational age was 38.3 (IQR [36,40]) weeks of amenorrhea. The rate of preterm birth was 28.6%, and the extreme gestational ages varied between 29.6 and 41.3

Table 3
Phenotype at first consultation.

	Number of completed case report form	*N* (%)
Neurological examination		
Hypertonia	21	2 (9.5)
Hypotonia	22	20 (90.9)
Axial hypotonia	22	16 (72.7)
Peripheral hypotonia	21	17 (81.0)
Distal muscle wasting and weakness	14	12 (85.7)
Tongue fasciculations	21	2 (9.5)
Weak cry	18	12 (66.7)
Respiratory disorders		
Apnea	21	10 (47.6)
Confirmed phrenic palsy	20	17 (85.0)
Possible phrenic palsy*	20	3 (15.0)
Unilateral phrenic palsy	19	16 (84.2)
Right hemidiaphragm	16	15 (93.8)
Thoracic deformities	18	5 (27.8)
Gastrointestinal disorders		
Dysphagia	19	11 (57.9)
Hypersalivation	20	5 (25.0)
Swallowing problems	19	7 (36.8)
Orthopedic examination		
Distal deformities	21	14 (66.7)
Metatarsus varus	21	10 (47.6)
Fatty finger pads	21	7 (33.3)
Hand arthrogryposis	21	7 (33.3)
Foot arthrogryposis	21	3 (14.3)
Spinal deformities	21	4 (19.0)
Dislocated hip	21	1 (4.8)

* The first case was suspected from recurring right lower lobe atelectasis or pneumonia, later disproved by chest scan. The second case also had unexplained opacity of the right lower lobe, with diminished movements of the right hemidiaphragm on fluoroscopy, and the last case had a subtle elevated right hemidiaphragm cupola. Nevertheless, none had been tagged with phrenic palsy on the forms.

weeks of amenorrhea. The APGAR score (Appearance, Pulse, Grimace, Activity, Respiration) at 1 minute was 9.2 (2.2) and at 5 minutes was 9.4 (1.8). IUGR was frequent and symmetrical: 63% of the children had a birth weight under the 10th percentile and length and head circumference values were 65% and 56% under the 10th percentile, respectively.

Newborn clinical examination was abnormal in almost half the cases (46%), invariably involving distal extremity features (metatarsus varus, arthrogryposis, or fatty finger pads). Nine children required neonatal unit hospitalization.

3.3. Clinical characteristics

3.3.1. At the first consultation

The reasons for the first specialist examination by decreasing order of recurrence were: respiratory failure (36.4%), failure to thrive (31.8%), stridor (27.3%), hypotonia (27.3%), phrenic palsy (9.1%) and distal deformities (9.1%). The clinical phenotype at that time is depicted in Table 3.

Fifteen of the 22 (68.2%) patients were said to be symptomatic (hypotonia, respiratory symptoms, areflexia or diaphragmatic paralysis) before 3 months old, yet only 8 of them (53%) obtained a specialist appointment before 3 months old. The overall median timeline for a specialist consultation was 1 month (IQR [0–3.1]). The median age, interquartile range and range of occurrence of the main clinical features are depicted in Fig. 2 in order to show the chronological succession of symptoms.

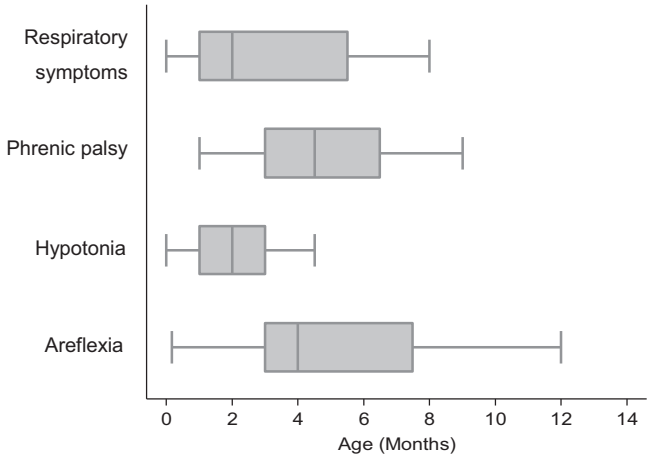

Fig. 2. Box plot of the time to occurrence of the main clinical features. This figure excludes 4 outside values.

Hypotonia occurred at a median of 2 months (IQR [0.2–4.3]) before the discovery of areflexia ($p < 0.01$) and the median age of the first respiratory symptoms was 1 month (IQR [0–2]) earlier than the age of phrenic palsy diagnosis ($p = 0.01$). The 3 children who had bilateral diaphragmatic paralysis did not seem to have an earlier onset of respiratory symptoms compared with the children with unilateral palsy (median: 2 months (IQR [1–3.5]) vs 3 months (IQR [1.7–6]); $p = 0.77$).

The patients who had shown distal deformities at birth did not develop earlier respiratory distress, as these symptoms appeared on average at 4 (3.1) months versus 2.4 (1.6) in the rest of the population ($p = 0.218$).

At the time of the first consultation, 67% and 75% of children had weight and length below the 10th percentile, respectively.

3.3.2. Clinical course

The disease progression is described in Table 4.

Autonomic neuropathy was suspected in 13 cases out of 19 (68.4%): heart blocks or arrhythmias ($N = 7$), constipation ($N = 7$), uropathy ($N = 5$), excessive sweating ($N = 6$), gastroparesis ($N = 4$) and high blood pressure ($N = 1$). In addition, one patient in this series had a pyramidal syndrome following acute anoxic events, and another was diagnosed with severe cognitive impairment for unknown reasons. Regarding social interactions, 7 of the 9 children who survived beyond the first 2 years were once able to speak (77.8%), 1 had taken part in normal classes, and 2 attended special classes.

No extrapyramidal cerebellar syndrome, cranial nerve involvement, auditory neuropathy, optic neuropathy, behavioral disorder or autistic disorder was reported.

Table 4
Clinical course.

	Number of completed report forms	*N* (%)
Neurological assessment		
Head holding	21	10 (47.6)
Sitting without support[1]	20	1 (5.0)
Learning to walk	20	0 (0.0)
Learning to speak by 2 years of age	9	7 (77.8)
Hypomimia	15	7 (46.7)
Brooke scale median [IQR]	15	6 [4- 6]
Vignos scale median [IQR]	16	10 [9–10]
Movement abilities against gravity		
in arms[2]	16	11 (68.8)
in legs	15	4 (26.7)
Seizures[3]	20	5 (25.0)
Normal cognition[4]	17	14 (82.4)
Respiratory symptoms		
Bronchial congestion or pneumonia	17	14 (82.4)
Orthopedic symptoms		
Scoliosis	20	9 (45.0)
Upper limb stiffness[5]	20	11 (55.0)
Lower limb stiffness[6]	20	11 (55.0)

[1] 1 isolated case of sitting without support at 12 months old.
[2] 3 cases lost this ability at 6, 7 and 27 months old.
[3] All appeared during or after hypoxic or anoxic episodes, 4 were generalized.
[4] Cognition was assessed from the subjective point of view of the practitioners, without recourse to psychometric testing.
[5] Claw hands in 50%, wrist retraction in 25%, shoulder stiffness in 0%, elbow stiffness in 15%.
[6] Claw toes in 25%, stiff ankles in 35%, knee stiffness in 15%, hip dislocation in 22%.

Regarding respiratory symptoms, the disease evolution was marked with the recurrence of bronchial congestion or pneumonia leading to a median hospital stay of 60 days (IQR [13–150]), which accounted for 15% (IQR [4.9–30.5]) of their lifetime. The respiratory condition of 15 of the 22 patients required artificial ventilation, either assisted (2 noninvasive ventilation and 4 continuous positive airway pressure) or controlled (intubation for 11 and tracheostomy for 8 children at a median age of 10 months (IQR [5–18]). Three out of 14 patients (21.4%), with precise information on the date of symptom onset, were dependent on ventilation within one month of onset.

In all patients, nutritional support was artificially provided enterally either by gastrostomy for 7 patients or a nasogastric tube for 15. Despite nutritional support, the last recorded weight was still under the 10th percentile in 6 out of 13 children.

3.4. Paraclinical investigations

3.4.1. Genetic results

Thirteen children out of 22 (59.1%) had compound heterozygous *IGHMBP2* mutations. The genetic results are represented in Fig. 3 and are listed in detail in Table 5.

Two cases were diagnosed by exome sequencing and 1 case by NGS gene panel.

3.4.2. EMG and NCS patterns

EMG data were recorded for 17 patients (77.3%) and performed at a median age of 4.8 months (IQR [3.4–5.8]) for the first study. It revealed a constant motor neuropathy (17/17), frequently combined with a sensory neuropathy (14/17, 82.4%). Demyelinating characteristics associated with the leading axonal involvement were present in 40% of the patients explored. Needle EMG revealed chronic and active denervation (11/16, 68.8%).

3.4.3. Other items

Muscle tissue, sampled from 11 patients and performed at a median age of 4.77 (IQR [3,375–5,75]) months, revealed a neurogenic muscular atrophy with a heterogeneous decrease in skeletal muscle fiber caliber and endoneurial fibrosis.

Only 4 nerve biopsies were achieved, one of which was not interpretable. They showed pictures of hypomyelination or demyelination, but no hypermyelination or remyelination. One isolated case of myogenic muscular atrophy was reported.

Magnetic resonance imaging of the brain was normal for 71.4% of the patients. Only non-specific features were revealed: a benign enlargement of the subarachnoid spaces in 3 cases and an apparent sequela of cerebral anoxia in one patient.

Liver function tests were abnormal for 9 out of 16 patients (56.3%), although CK levels were normal or slightly elevated (452 UI/l maximum). Metabolic balance showed non-specific results: there was one case of an unexplained high rate of sialic acid in urine, one case of transient hyperlactatemia and another case of hyperammonemia.

The echocardiography was normal for all but 1 of 15 patients, who showed a benign atrial septal defect.

3.5. Survival results

The median duration of follow-up from birth was 113 months. Death occurred in 16 patients and overall survival at 12 months was 41%. All survivors beyond 32 months old were tracheostomized. Among the 8 patients with a tracheostomy, 2 died, 1 due to a sudden tracheal hemorrhage and the other following palliative care. Median overall survival was 5 months (IQR [4–7]) for the children who did not receive ventilatory assistance by tracheostomy, and this was not reached (IQR [96-not reached]) for those who did (Fig. 4).

Due to the high impact of tracheostomy on life expectancy, we excluded children with a tracheostomy from further analyses in order to study the natural course of the disease.

Overall survival was prolonged when age at first examination was greater than 3 months ($p < 0.01$) and also when symptom onset appeared after 3 months of life (Fig. 5).

No survival difference was found according to the allelic status ($p = 0.70$) or the existence or not of a nonsense mutation ($p = 0.52$). Neither preterm birth ($p = 0.87$) nor

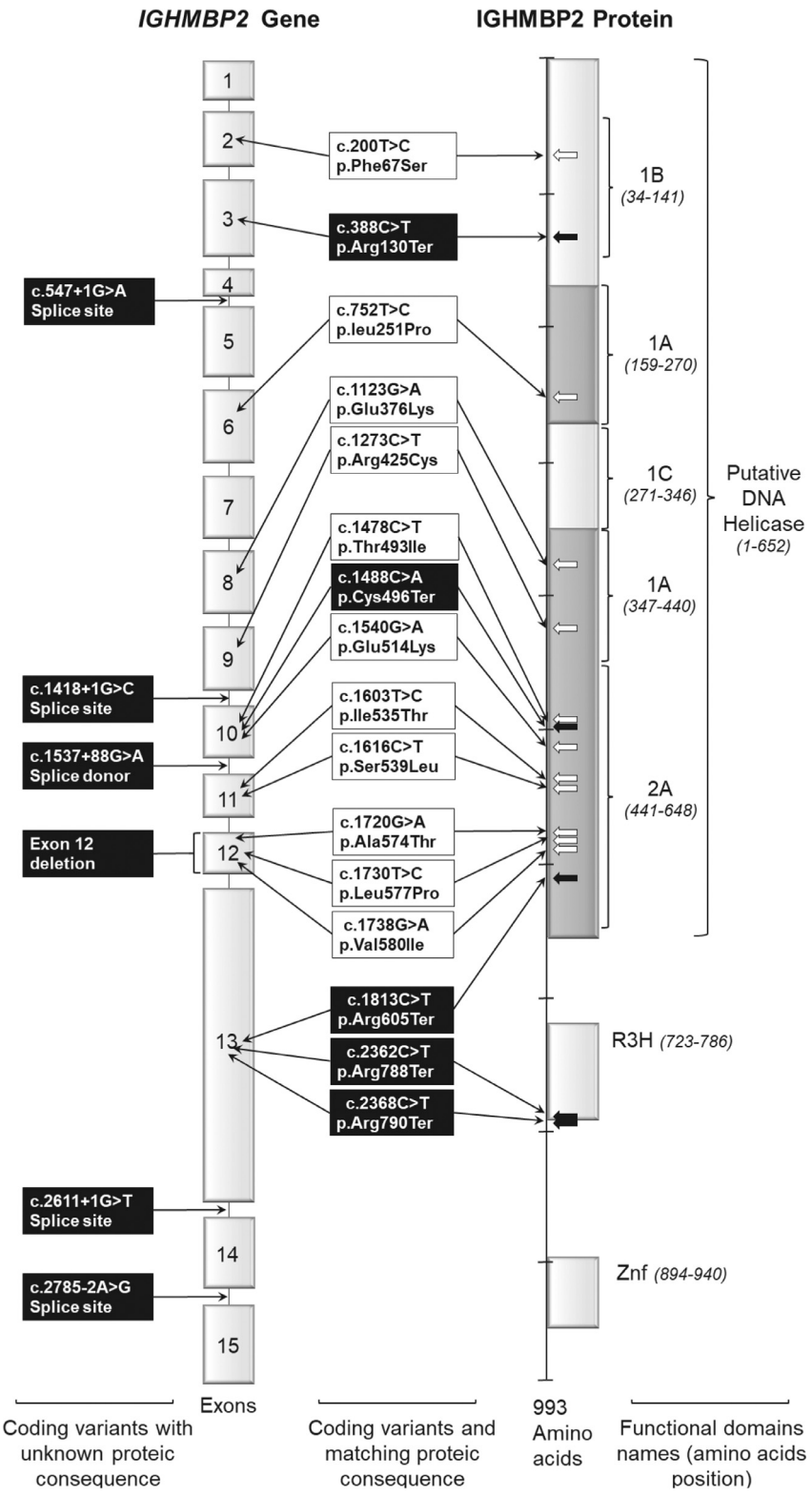

Fig. 3. Gene *IGHMBP2* and variants. Legend: Truncating mutations are shown in black (nonsense and frameshift mutations like splice site and deletions, as they must cause a premature stop codon), while missense mutations are in white. The gray functional domain refers to where the ATP binding sites particularly concentrated [45]. The coding variants and matching proteic variants are represented in line with the Human Genome Variation Society recommendations [41]. "c." refers to the coding sequence of DNA: ">" means a translocation between two nucleobases (see 1984 nomenclature [46]) and "del" a deletion; "+" was used when an intronic mutation occurred after the end of an exon and a certain amount of nucleobases and "−" when it occurred just before an exon. "p." refers to the proteic consequence: a change in amino acid (see 1983 nomenclature [47]) or "Ter" when it produced a stop codon. Note: Graph designed on the basis of the following references: [23,44,45,48].

Table 5
List of NM002180.2 (*IGHMBP2*) variants by order of position in DNA.

Coding variant	Matching proteic variant	Conse-quence[1]	Conservation across species	Already posted in databases[2]	Case n°	International classification[3]
c.200T > C	p.Phe67Ser	MS	Poorly conserved	No	5, 12	3
c.388C > T	p.Arg130Ter	NS		Yes (14) (18)	7	5
c.547 + 1G > A	UK	S		No	8	4
c.752T > C	p.Leu251Pro	MS	Wellconserved	Yes (43)	13	4
c.1123G > A	p.Glu376Lys	MS (A→B)	Well conserved	No	10	4
c.1273C > T	p.Arg425Cys	MS	Highly conserved	Yes (22)	14, 16	4
c.1418 + 1G > C	UK	S		No	9	4
c.1478C > T	p.Thr493Ile	MS	Highly conserved	Yes (3) (48)	6, 21	5
c.1488C > A	p.Cys496Ter	NS		Yes (8) (18) (23) (43) (14) (19) (30)	6, 7, 18, 21, 22	5
c.1537 + 88G > A	UK	DI		No	12	3
c.1540G > A	p.Glu514Lys	MS (A→B)	Highly conserved	Yes (12) (48)	11	5
c.1603T > C	p.Ile535Thr	MS	Well conserved	No	18	3
c.1616C > T	p.Ser539Leu	MS	Poorly conserved	No	1, 2, 3, 4, 15, 19	4
c.1720G > A	p.Ala574Thr	MS	Well conserved	No	16	3
c.1730T > C	p.Leu577Pro	MS	Quite conserved	Yes (18) (43) (3)	13	5
c.1738G > A	p.Val580Ile	MS	Highly conserved	Yes (12) (3)	20	5
UK	Exon 12 deletion[4]	DII		No	8	5
c.1813C > T	p.Arg605Ter	NS		Yes (18) (14)	10	5
c.2362C > T	p.Arg788Ter	NS		Yes (18)	11	5
c.2368C > T	p.Arg790Ter	NS		Yes (43)	17	5
c.2611 + 1G > T	UK	S		Yes (12)	14, 17	5
c.2785–2A > G	UK	S		Yes (19)	22	5

"UK" when the precise consequence of an intronic mutation is unknown.

[1] Missense (MS), nonsense (NS), splice mutation (S), deep intronic mutation (DI). "A→B" means an acid amino acid becomes basic.

[2] The numbers between square brackets are bibliographic references.

[3] Each mutation was labeled as "pathogenic" (5), "likely pathogenic" (4), "uncertain significance" (3), "likely benign" (2), or "benign" (1).

[4] According to the RNA sequencing result, the causal deep intronic mutation could not be identified because post-mortem DNA material was lacking.

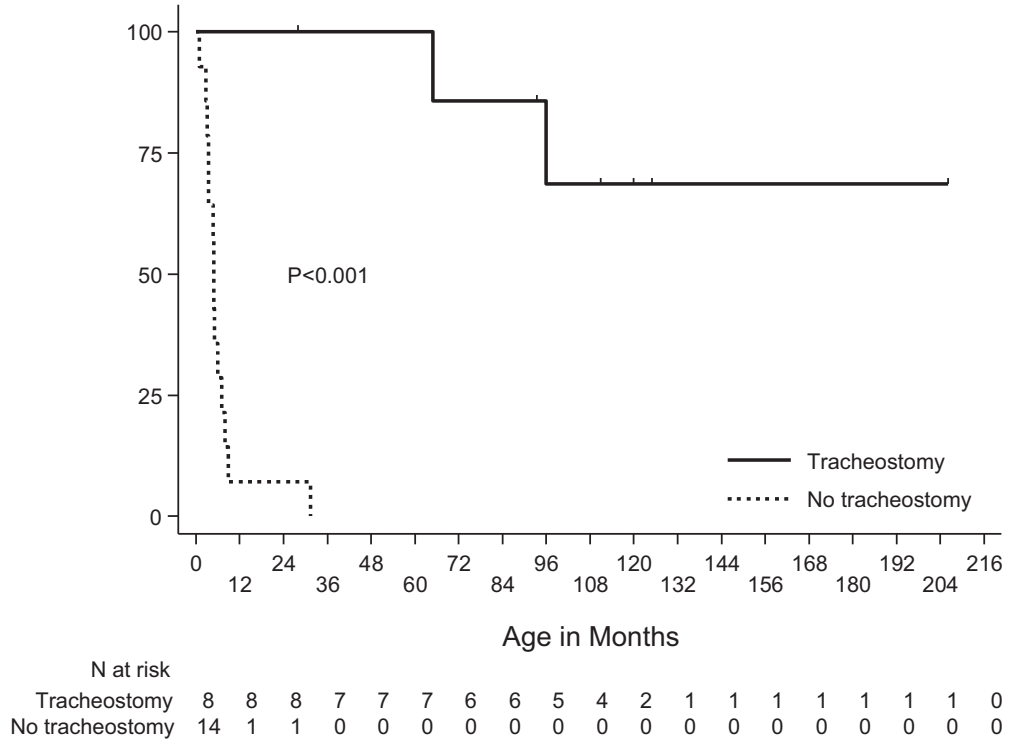

Fig. 4. Kaplan–Meier curves for overall survival of children with and without a tracheostomy.

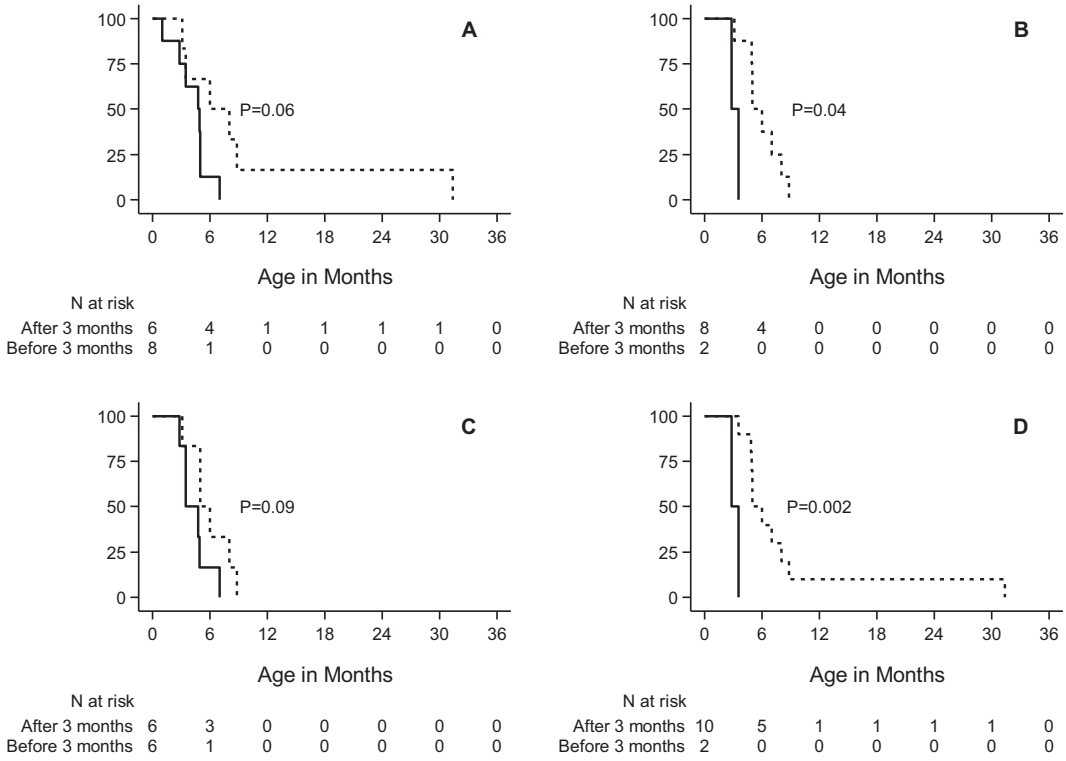

Fig. 5. Kaplan–Meier curves for overall survival according to age at appearance of (A) hypotonia, (B) areflexia discovery, (C) first respiratory symptoms, and (D) phrenic palsy. *Legend: Dashed lines represent onset of symptoms after 3 months; solid lines represent onset of symptoms before 3 months.*

IUGR under the 10th percentile ($p = 0.12$) influenced the prognosis.

Limitation of life support was recommended to families after a multidisciplinary meeting in 77.3% of cases (17/22). For the 8 tracheostomized patients, palliative care was first suggested to 4 families, 2 of which declined and requested the tracheostomy. The remaining 2 families accepted palliative care much later following repeated cardiovascular collapse.

4. Discussion

This was the first national multicenter study investigating SMARD1 epidemiology in France.

Our data cover a large retrospective period, beginning with the gene discovery in 1999 [11]. We describe this condition in as much detail as possible so that medical practitioners will have the necessary elements to improve the diagnostic approach and provide optimal follow-up and care. Our observations were comparable to those in the medical literature [3,23,44,49]. The study limitations were the retrospective design and the relatively small sample despite our efforts to record every French case of this very rare disease. While, the incidence of non-genotyped cases is difficult to assess as there is no specific symptom.

Our findings enhance and challenge the diagnostic criteria published by Pitt et al. in 2003 [23] and the algorithm of Guenther et al. from 2007 [14]. For example, we observed that many cases from our cohort would have been excluded according to items (i) (ii) and (iv) (see Table 1, column "Clinical criteria") although their genotype, phenotype and natural course matched with others. More specifically, IUGR under the 10th percentile seems less restrictive than the 3rd percentile (60 vs. 45%), 31.8% developed symptoms after 3 months of age, and ventilator dependence occurred mostly (78.6%) after one month of disease evolution.

Furthermore, item (iii) "Diaphragmatic weakness" should not be compulsory in view of our results, as it was detected belatedly after the respiratory symptoms. Thus, rather than waiting for the occurrence of phrenic palsy to raise the possibility of SMARD1, practitioners should order genetic testing, keeping in mind that this feature will very likely appear at some point. This delay might be explained by an early but progressive phrenic palsy causing weak cry and feeding difficulties, followed by respiratory symptoms and ultimately radiographic evidence. A trigger factor, like an infection, could hasten acute respiratory failure. In the meantime, there are many options for monitoring diaphragmatic function: maximal transdiaphragmatic pressure, diaphragmatic muscle tone, respiratory inductive plethysmography, diaphragm ultrasonography, blood gas carbon dioxide level, and simply oxygen saturation with pulse oximetry. In the case of school-aged children (at least 4 years), forced vital capacity, maximal inspiratory airway pressure and sniff nasal inspiratory pressure may be more suitable [50]. Some might think the delay is the consequence of belated radiological examination. We cannot clearly disprove this, but we do underline that the

first chest X-ray at the onset of respiratory symptoms was normal for at least 4 patients.

For undetermined reasons, a substantial majority showed right unilateral phrenic paralysis, whereas non-SMARD1 patients tend to show left paralysis [51,52], generally caused by surgery or tumor. In such circumstances, bilateral phrenic palsy is said to be more severe [51] and unilateral palsy "paucisymptomatic." This clearly did not apply to our SMARD1 children, in agreement with previous publications [10,24,27] except for the report of two exceptional cases, where phrenic palsy remained silent for several years [27,26]. Thus, the phrenic nerves might not be the only respiratory nerves involved in SMARD1, contrary to what is widely assumed [2,28]. Another possibility is that bulbar function is also impaired, earlier than expected in comparison with SMA, and that this contributes to the failure to thrive.

Along the same lines, areflexia was noted much later than hypotonia, which reflects the progressive nature of this neuropathy.

Stridor was the third reason for the initial specialist consultation, the same as hypotonia, which was also reported by Stalpers et al. [49].

We confirm the previous observation of a tendency toward increased rates of preterm birth (28.6% versus a national rate of 7.3% in 2012 [53]), IUGR under the 10th percentile, and distal deformities. The underlying reason might be an antenatal gene expression of *IGHMBP2*, although these early symptoms were not associated with a more pejorative outcome.

In brief, clinicians should consider genetic study of *IGHMBP2* not only in cases of phrenic palsy and areflexia. They should be alerted early on by distal deformities in a premature newborn with symmetrical IUGR under the 10th percentile and respiratory warning signs (weak cry, stridor and feeding difficulties), and this all the more so in a consanguineous family. These data are consistent with previous publications [20,49].

Paraclinical investigations can assist in diagnosis, and electrophysiological and histopathological results seem to be particularly relevant. EMG and NCS consistently showed abnormal features, with motor neuropathy seeming imperative and axonal involution characteristic, although sensory neuropathy and demyelination were quite frequent. Similarly, nerve and muscle biopsies showed pictures of axonal degeneration [54] and demyelination (unlike Pitt's histopathological criterion, item (iii); see Table 1). In this regard, accurately naming this disease has been particularly difficult. For example, "distal hereditary motor neuropathy type VI" might be misleading as it does not include the sensory pattern, and "spinal muscular atrophy with respiratory distress 1″ does not include the term "neuropathy." In addition, MRI, CK dosage and metabolic balance may all be helpful for differential diagnoses. There were no cases of dilated cardiomyopathy, unlike with the nmd mouse [2].

Overall survival was significantly shortened in patients who had a specialist examination, areflexia, or diaphragmatic paralysis before 3 months old. Only 1 patient lived more than 9 months without artificial ventilation; he reached 31 months of age but died of respiratory failure under palliative care. These findings, in line with previous publications [2], prompt us to propose three subtypes of SMARD1: early-onset (less than 3 months old, more severe), the classical onset (more than 3 months old, but still severe), and late-onset (eventually less severe, very rare, and needing further definition; for instance, when there is no permanent ventilator dependence, or when it occurs after 12 months old). Identifying such predictive factors might help family members and medical practitioners to think ahead about therapeutic options.

In the coming years, with the wider application of NGS for the analysis of large panels of genes of interest and whole exome sequencing, unsuspected diagnoses might be revealed [55] and the phenotype of SMARD1 might be reshaped. For example, Cottenie et al. in 2014 [56] performed exome sequencing and depicted 11 families affected by Charcot–Marie–Tooth disease type 2 (CMT2, axonal) with recessively inherited *IGHMBP2* mutations. The affected individuals gradually developed muscle weakness and wasting, and sensory loss started between 1 and 10 years old, but none showed significant respiratory symptoms or phrenic palsy, nor did they require respiratory support. Fibroblast and lymphoblast study showed higher residual levels of IGHMBP2 enzymatic activity, just as Eckart et al. [3] had demonstrated 2 years earlier in less severe courses of SMARD1. They followed survivors beyond 1 year old for 7.8 years, and a higher residual level of IGHMBP2 protein activity predicted better prognosis. Guenther et al. had similar results [14,26]. Conversely, a low level might indicate a more severe phenotype, as in a neonatal case [30]. Thus, a clinical continuum has emerged between SMARD1 and what is now called CMT2S (or AR-CMT2S [57–60]).

In our retrospective cohort, there were no such dosage studies. Yet given the phenotypic heterogeneity associated with *IGHMBP2* mutation, it may be important – although technically challenging – to do so in order to prove its discriminative value as a prognostic factor on a larger scale. This would be particularly crucial in ambiguous cases between late-onset SMARD1 [4,26–29] and CMT2S, since the respiratory issue depends on it. In the meantime, we suggest monitoring with pulmonary function testing, chest radiography, fluoroscopy, spirometry and/or the sniff test (from the age of 6 [50]) at regular intervals. For this reason, we chose to exclude patients without respiratory symptoms as we assumed they might bias our results, having forms of CMT2S instead of late-onset SMARD1, which accurately stands for "SMA with respiratory distress."

It would have been interesting to make a direct comparison of the clinical and genetic phenotypes of these two conditions. However, the time required to classify them seemed insufficient and would have led to non-homogeneous and skewed groups. Indeed, the latest significant age of the first acute complication reported in the late-onset SMARD1 subtype was 6 years and 4 months ([49] unexpected death while sleeping), and 9 of the 22 patients of our cohort were

born fewer than 6 years before the data collection period began. Beyond this age, we found no occurrences of sudden respiratory failure [2,31,49].

Regarding the molecular diagnosis, we recorded a total of 21 variants of the *IGHMBP2* gene, including 8 newly discovered ones. The SMARD1 causal mutations concerned the DNA helicase domain, except for 4 that produced truncated proteins anyway. If we take into account only missense mutations, most of them (88.9%) were located where the ATP binding sites are concentrated (domains 1A and 2A [17], see Fig. 3) versus 64% in the cases of AR-CMT2S [56], whereas truncating mutations seemed to concern only the distal end of the protein in the AR-CMT2S cases. This information may provide valuable assistance in genetic counseling.

Six out of twenty-two patients had the same homozygous *IGHMBP2* mutation (c.1616C>T predictive of the p.Ser539Leu substitution) affecting a highly conserved nucleotide. The genetics research group of Necker hospital investigated five of these cases who are unrelated Algerian patients, mainly from Kabylia. They launched a linkage analysis which revealed a common haplotype, suggestive of a founder effect estimated to be 35 generations old using the ESTIAGE program [61]. The variant consistently segregated with the disease and was not identified in 120 control chromosomes from Algerian population.

Some of our patients could not be diagnosed with standard sequencing, with 2 cases diagnosed through exome sequencing and another by an NGS gene panel. If the clinical suspicion is strong, further analyses are required. NGS techniques are automated and cheaper than Sanger sequencing, but panels imply the processing of a large volume of information and difficulties in data management, and thus are not necessarily time-saving as a first-line strategy.

Two siblings of our cohort, carrying the same homozygous mutation, developed diametrically opposed symptomatology. One presented with respiratory symptoms at 3 months versus 31 months for the second, even though they carried the exact same mutations, as Joseph et al. 2009 [31] previously described. The Mnm gene (modifier of neuromuscular degeneration) on chromosome 13 might also play a part as it seems to lessen the motoneuron involution and improve the clinical outcome in the nmd mouse [62], interacting with epigenetic factors.

With regard to SMARD1 management, the overall natural course was marked with severe motor impairment with lower-extremity predominance, a recurrence of life-threatening bronchial congestion, and symptoms like autonomic neuropathy. Among the various modes of ventilation, only tracheostomy managed to substantially extend life expectancy. Nevertheless, tracheostomy ventilator dependency requires daily care over the patient's lifetime, and both parents and medical practitioners should take this into account before making such a decisive choice. In our study, multidisciplinary meetings often took place to discuss halting treatment, but less often in the tracheostomized population.

This is all the more important as the data concerning central nervous system involvement is conflicting. We found fewer seizures than Eckart et al. in 2012 [3], 20% versus 50%. Cognition seemed to be normal (82.4%), although suitable psychometric tests would be required to confirm this, whereas Eckart et al. in 2012 reported 30% cognitive impairment, based on the subjective opinions of relatives. Concerning social interaction, most survivors beyond 2 years old were able to talk and had normal facial expressions, but few of them had access to education, which might be multifactorial. MRI showed no significant abnormalities [63], except after acute hypoxic respiratory failure(s). [31] Further studies are warranted to properly evaluate cognition and the quality of life of tracheostomized SMARD1 patients.

SMA is more common than SMARD1 and support might coincide to some extent. The 2007 "Consensus Statement for Standard of Care in SMA" [64] stated that correct management requires that both medical practitioners and family members anticipate future needs as soon as possible. Care options should be explained in an impartial way and medical professionals should facilitate home care rather than lengthen intensive care unit stay. Nevertheless, health practices have changed and the recent commercialization of a curative medicine for SMA (Nusinersen) is currently disrupting these assumptions. Following the SMA model, preclinical research in SMARD1 has made significant headway in the last few years. Various approaches are now being considered: gene therapy relying on a viral vector, which helps cross the brain blood barrier (self-complementary adeno-associated virus, serotype 9: scAAV9); pharmacological treatment (monoclonal antibody binding to tyrosine kinase C receptor: Mab2256, and polyethylene-glycol coupled with insulin growth factor 1); and stem cell therapy based on the transplantation of aldehyde dehydrogenase stem cells with high side scatter and low activity, healthy induced pluripotent stem cells, or corrected SMARD1 cells [65].

SMARD1 is a severe progressive congenital neuromuscular disease whose diagnostic criteria need to be reconsidered, according to this national retrospective study. In its most classical form, this condition leads to premature death before a child is 1 year old, but the phenotype remains heterogeneous, which raises ethical issues. We highlight the fi that the prognosis of the early-onset subtype is even worse. Proper cognitive and quality of life evaluation, combined with key elements for early diagnoses, are the indispensable tools for informed decision-making about life support.

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