Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 27 (2017) 596–605

www.elsevier.com/locate/nmd

Workshop report

218th ENMC International Workshop: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19–21 February 2016

Richard S. Finkel [a], Thomas Sejersen [b], Eugenio Mercuri [c,*] on behalf of the ENMC SMA Workshop Study Group [1]

[a] *Pediatric Neurology, Nemours Children's Hospital, Orlando, FL, USA*
[b] *Pediatric Neurology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden*
[c] *Pediatric Neurology, Policlinico Gemelli, Catholic University and Centro Nemo, Rome, Italy*

Received 15 February 2017

1. Introduction

Twenty-six researchers and industry representatives from nine different countries (USA, Spain, Italy, France, Germany, Switzerland, Sweden, The Netherlands, United Kingdom), one patient and representatives of SMA Europe and from the SMA Foundation met in Naarden on the weekend of the 19–21 of February 2016 to update current knowledge on standards of care (SOC) for spinal muscular atrophy (SMA).

2. Background

Spinal muscular atrophy (SMA) is a monogenic disorder, due to the mutations in the survival of motor neuron (*SMN1*) gene (5q11.2-q13.3). SMA has an incidence of about 1 in 11,000 live births [1]. It includes a wide range of phenotypes: very weak infants unable to sit unsupported (type 1), non-ambulant children able to sit independently (type 2), up to ambulant children (type 3) and adults (type 4) [2,3]. These maximal motor milestones may be lost over time (Table 1).

Following recommendations at an International Conference on the Standard of Care for SMA in September 2004 [5], a SMA standard of care committee was established and worked from January 2005 to create a consensus statement on SMA until publication of the report in August 2007 [6]. The core committee consisted of 12 expert clinicians in SMA (11 neurologists, 1 pulmonologist) and three consultants (1 from NIH, 2 from patient advocacy groups). Four working groups were established, each with a European and US co-leader, and addressed diagnostics/new interventions, pulmonary care, gastrointestinal/nutritional care, and orthopedic care/rehabilitation. Palliative care was added subsequently. Six to eleven experts in these topics were then invited to participate in each working group. The committee identified the following goals for all four working groups: (1) to identify current care issues in SMA clinical practice, (2) to search for existing practices in SMA clinical care and the rationale or data supporting such practices, (3) to achieve consensus of the most appropriate medical practice in caring for patients with SMA, (4) to use this standard of care consensus to establish clinical care guidelines for future SMA clinical trials, (5) to identify future research directions in the care of SMA patients, and (6) to publish the consensus as guidelines for clinical care of SMA patients. Each working group then performed a detailed literature search and conducted conference calls to discuss their topics [6]. The Delphi technique was used to explore consensus expert opinion [7]. The goal of the Delphi technique is designed to identify if, in aggregation, there is a rank-ordered cluster of answers to a particular question from respondents that reflects group consensus. It also serves to identify if no consensus is present and where topics need further study. At least two rounds of the Delphi were performed for each specific question that was addressed. In addition, two in-person conferences were conducted to discuss the topics in an open forum and settle upon an agreeable written summary. Following publication of the report in 2007, the SMA SOC guidelines were widely adopted by SMA clinical care centers and have been promoted by patient advocacy groups since. Additionally, they were often included by pharmaceutical companies in clinical trial protocols as a benchmark for care during participation in a clinical trial.

Over the last decade many aspects of care for infants and children with SMA have dramatically improved, resulting in

* Corresponding author. Pediatric Neurology, Policlinico Gemelli, UCSC, Largo Gemelli, 00168 Roma, Italy. Fax: +39 06 30154363.
E-mail address: mercuri@rm.unicatt.it (E. Mercuri).

[1] ENMC SMA Workshop Study Group: Bertini E, Chen K, Crawford T, Dubowitz V, de Lemus K, Graham R, Hurst Davis R, Iannaccone S, Kirschner J, Main M, Mayer OH, Mazzone E, Mitchell J, Montes J, Muntoni F, Murphy A, Quijano-Roy S, Robertson A, Schroth M, Simonds AK, Snyder B, Vitale M, Wittchen A, Woods S, Qian Y, Wirth B.

http://dx.doi.org/10.1016/j.nmd.2017.02.014

Table 1
Clinical classification criteria for spinal muscular atrophy [4].

	Age at symptom onset	Highest function achieved
Type 1 (Werdnig–Hoffmann disease)	0–6 months	Never sits or rolls over
Type 2 (intermediate)	7–18 months	Sits, may stand, never walks
Type 3 (mild, Kugelberg–Welander disease)	>18 months	Walks
Type 4 (adult)	2°–3° decade	Walk unaided

longer survival and better quality of life. Several papers have reported a large amount of data reflecting improvements in care in orthopedic management of scoliosis, nutrition, respiratory support and other aspects [8–14]. In recognition of these changes in the care of patients with SMA, it was felt that an update of SOC was needed. We proposed a new workshop that would comprehensively review the recent literature and take into account experts' opinions on current standards of care.

The aims of this workshop were:

a. Examine each of the clinically meaningful topics of care for a patient with SMA and expand upon the number of areas of discussion from the initial 2007 effort.
b. Identify areas where consensus can be easily obtained based on striking evidence from published studies and to try to identify the best standards of care available. The relative degree of support and the estimated importance of an intervention would be developed for each recommendation.
c. Promote discussion among experts, identifying the areas of controversy that warrant further study.
d. Include patients in this process and request comments from pharmaceutical companies with drugs under clinical development for SMA.

An international steering committee identified 9 topics to be addressed:

1 Diagnosis and genetics
2 Nutrition, Growth and Bone Health Care
3 Pulmonary Care
4 Orthopedic Care
5 Physical Therapy and Rehabilitation
6 Other organ system involvement
7 Acute care in the hospital setting
8 Medication
9 Ethics and palliative care

Two leaders were then invited to head each topic, in most cases one from Europe and one from the United States. The WG leaders in turn were tasked to invite approximately ten clinicians with expertise in SMA, balancing participation from Europe and other countries. Each WG, if appropriate to the topic, was encouraged to include at least one patient or parent/caregiver of a child with SMA to participate in the discussion. Similarly, representatives of the six pharmaceutical companies with drugs in clinical development for SMA were invited to review the drafts of the WG's deliberations and provide comment. The WG leaders, WG participants, patient advocacy representatives, patients/parents and industry participants are listed in the Appendix S1.

This workshop was preceded by 2 conference calls, and at least 2 web-based Delphi rounds of inquiry by each working group (WG). The coordinators participated in all WG to ensure homogeneity. The first round of Delphi inquiry was designed to generate specific topics from open-ended questions. The second round focused on the topics having the most common interest to the WG and ranked the highest on the first round. Ying Qian (SMA Foundation) provided analytical support and Becca Leary from TREAT NMD provided organization support to several of the working groups.

The initial consensus from these working groups was then presented at the Workshop for further discussion by the entire group and finalized for the publication.

When needed, further Delphi rounds were performed following the Workshop.

Each topic was summarized as to where:

- Consensus is reached with uniform opinion
- Consensus is reached with a majority opinion, and with minority opinions mentioned
- No consensus is reached and more work needs to be performed

The American Academy of Pediatrics policy statement: classifying recommendations for clinical practice guidelines (2004) was used as the structure for each working group to derive a specific recommendation as to the quality of the evidence in the literature, the relative strength of the recommendation as to providing benefit or harm [15]. Per these guidelines, "a strong recommendation means that the committee believes that the benefits of the recommended approach clearly exceed the harms of that approach (or, in the case of a strong negative recommendation, that the harms clearly exceed the benefits) and that the quality of the evidence supporting this approach is either excellent or impossible to obtain. Clinicians should follow such guidelines unless a clear and compelling rationale for acting in a contrary manner is present. A recommendation means that the committee believes that the benefits exceed the harms (or, in the case of a negative recommendation, that the harms exceed the benefits), but the quality of the evidence on which this recommendation is based is not as strong. Clinicians also generally should follow such guidance but also should be alert to new information and sensitive to patient preferences."

2.1. Topics discussed

2.1.1. Setting the framework: 1. Natural history and standards of care

The natural history of type 1, 2 and 3 SMA was discussed, focusing on how this has evolved in parallel with evolving standards of care.

Richard Finkel presented a review of published data on survival for SMA types 1, 2 and 3 [16]. Table 2A,B highlights the historical and recent data showing how survival depends

Table 2
(A) Natural history studies in SMA type 1 [16]. Published studies are listed by first author, year of publication and years when the data were collected, country where data were collected, type of study, level of supportive care provided, survival and mortality data. (B) Survival probabilities of patients with SMA Types II and III [16]. (C) Ambulatory probabilities of patients with SMA Type III from reports where *SMN2* copy number is not known [16].

A

Study lead author, year of publication Years when data were collected Country	Study type	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Descriptive case series. No or little genetic confirmation. Age of onset was generally less than 6 months of age. Little or no supportive care was provided.				
Brandt, 1950 [17] Denmark	ERS, R N = 76 of 112	None		56% died by 12M of age 80% died by 4 years of age
Byers and Banker, 1961 [18] 1950–61 USA	SS, R N = 52	None	2 survivors, M = 17	Symptom onset <2 months (Types IA and IB): 23/25 died, 2 sat, M = 10 (0.5–52) Symptom onset 2–12 months (Types IC and II): 5 of 19 died, M = 25 (7–73)
Pearn and Wilson, 1973 [19] 1961–70, England	SS, R N = 76	None	None live >3 years	M = 5.9, m = 7 95% died by 18 months
Thomas and Dubowitz, 1994 [20] 1982–90 England	SS, R N = 36	None	"few live beyond 2 years"	(n = 29) M = 9.6 , m = 7 (1–24) Symptom onset <2 months: m = 5.5 Symptom onset >2 months: m = 17
Ignatius, 1994 [21] 1960–88 Finland	ERS, R N = 71	None	Uniformly poor if symptoms onset <2 mos, variable if onset 2–6 mos	(n = 69) M = 8.75, m = 7. Age at symptom onset and median age at death: birth, m = 4; 1–2 months, m = 7.5; 4–6 months, m = 17.5
Zerres et al., 1995 [22] 1985–95 Germany	ESR, R N = 197 + 90	Minimal	2 years = 32% 4 years = 18% 10 years=8% 20 years =0	
Borkowska, 2002 [23] Poland and Germany	ERS, R N = 349	Minimal	10% lived >5 years	(n = 18) M = 11 (3.4) years (5–24 years)
Case series with some genetic confirmation and SMN2 gene copy number. The extent of supportive care varied.				
Chung, 2004 [32] 1984–2002 Hong Kong	SS, R N = 22	Proactive	6 survivors, all NIV/TV dependent: 1Y = 50% 2Y = 40% 4Y,10Y, 20Y = 30%	16 of 22 (72%) died, m = approximately 2 years
Ioos, 2004 [27] France	SS, R N = 68	Proactive	IB: 18% alive with TV (8–17Y) IC: 74% alive (? range)	Age at symptom onset and median age at death: IB: (n = 27 of 33, 82% mortality), M = 18 (29) IC: (n = 9 of 35, 26% mortality), M = 4 Years (3.75Y)
Barois, 2005 [33] 1997–2004 France	MS, P IB = 14, IC = 32	Proactive	IB: 100% at 4Y IC: 94% at 4Y	
Bach, 2007 [34] 1996–2006 USA	SS, R N = 74 +18	Proactive	61 of 74 alive at M = 66.1 ± 44.8	Unsupported (n = 18), M = 9.6 ± 4.0 Supported (n = 74), 13 died: M = 32.9 ± 50.4, one at 270
Oskoui, 2007 [8] 1980–94 (n = 65) 1995–2006 (n = 78) USA mainly	ERS, R N = 143	2 cohorts: None Proactive	m = 8.5 m = indeterminate	M = 19.1, m = 7.3 (1.0–193.5) M = 22.1, m = 10.0 m (2.5–112.0)
Cobben, 2008 [31] 1996–99 Netherlands	SS/ESR, P N = 34	Minimal	26% survive to 1Y	Entire group: M = 6 (CI: 5–7), m = 10 Those with SMN2CN of 2 (n = 23): M = 6.7
Mannaa, 2009 [11] 1989–2005 USA	SS, R N = 15	Proactive	53% survivors: 2Y = 62% 4Y = 62% 10Y = 8%	Data not available
Park, 2010 [35] 2000–09 Korea	SS, R N = 14	57% with ventilation and feeding support	M = 22.8 (2.0) 6m = 93% 12m = 93% 18M = 76% 24M = 76% 30M = 65%	4 of 14 died, range 4–26

(*continued on next page*)

Table 2 (*continued*)

A

Study lead author, year of publication Years when data were collected Country	Study type	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Rudnik-Schoneborn, 2009 [25] 2000–05 diagnosis Germany	ERS, R N = 66	Variable NIV/TV, strong NG/GT support	Alive at 2: Overall: 6% SMN2CN2: 2% SMN2CN3: 67%	Mortality in 57 (86.3%): All patients: M = 7.3 (few days to 34 months), m = 6.1 SMN2NC = 2 (n = 57): M = 7.8, m = 6.5 (0.5–30) SMN2CN = 3 (n = 5): M = 28.9, m = 19 (10.1–55.1)
Lemoine et al., 2012 [24] 2002–09 USA	SS, R N= 49	2 groups: Proactive Supportive	4 year survival: Proactive: 72% Supportive: 33%	Proactive care (n = 23; 6 deaths): m=7.6 (IQR 6.5,10.5) Supportive care (n = 26; 16 deaths), m = 8.8 (IQR 4.7, 23.7).
Ge, 2012 [26] 2003–08 birth year, followed to 2010 China	ERS, R	Minimal	31.8% alive m = 10 (14–151) 1 year = 45% 2 years = 38% 4 years = 33% 5 years = 29% 10 years = 20%	68.2% died, M = 11.3 (15.0), m = 7.0 Symptom onset <2 months (n = 36), m = approx 6 Symptom onset ≥2 months (n = 37), m = approx 36
Farrar, 2013 [36] 1995–2010 Australia	SS, R N=20 Type I	Minimal 5% with GT and NIV	Survival at 1 year = 40% 2 years = 25% 4 years = 6% 10 years = 0	95% died, m = 7.4 (3–56)
Petit, 2011 [29] France	MS, R N=45 Type I	Minimal None of the survivors >2 years had prior GT or NIV/TV support	9/34 (26%) survived to 2 years SMN2CN = 2 (n = 1): 12% at 2 years SMN2CN = 3 (n = 8): 90% at 2 years	Mortality in 76%, M = 10.7 (10 days to 6.5 years) SMN2CN = 1: M = 4 (1 day to 11 months)
Finkel, 2014 [28] 2005–09 enrollment Followed for up to 3 years	MS, P N = 34	Proactive 76% with both GT and NIV/TV	Combined endpoint: Type IB, m = 11.9 Type IC, m = 13.6	Death (n = 9): m = 9 (2–14) Death or requiring >16 hours of BiPAP/day: Overall group: 13.5 m (IQR: 8.1–22) SNM2CN = 2: 10.5 m (IQR: 8.1–13.6 m)

B

SMA type II	Survival probability (%)								
	1 y	2 y	4 y	5 y	10 y	15 y	20 y	25 y	40 y
Zerres, 1995		100	100		98		77		
Zerres, 1997 [37]				98.5	97.8	82.8	75.1	68.5	
Mannaa, 2009 [11]		100	100		100				
Ge, 2012 [26]	100	100		97					
Farrar, 2013 [36]	100	100	97		93		93		52

SMA type III	Survival probability (%)						
	1 y	2 y	4 y	5 y	10 y	20 y	40 y
Mannaa, 2009 [11]		100	100		100		
Ge, 2012 [26]*		100	100	100	100	100	
Farrar, 2013 [36]							
IIIa	100	100	100		100	100	100
IIIb	100	100	100		100	100	

(*continued on next page*)

Table 2 (*continued*)

C

	Ambulatory probability							
	Age in years or years after disease onset							
	2 y	4 y	10 y	20 y	30 y	40 y	50 y	60 y
SMA type III								
Russman, 1983[a]				0[b]				
SMA type IIIa								
Zerres, 1995[c]	98%	94.5%	73%	44%		34%		
Russman, 1996[d]	90%	80%	57.5%	30%	30%	0%		
Zerres, 1997 [37]			70.3%	33.5%	22%	22%		
Ge, 2012 [26]	92%	92%	76.7%					
SMA type IIIb								
Zerres, 1995	100%	100%	97%	89%		67%		
Russman, 1996	100%	100%	85%	67.5%	52.5%	52.5%	17.5%	0%
Zerres, 1997 [37]			96.3%	84%	70.2%	58.7%		

SS, single site study; MS, multiple site study; ERS, epidemiological registry survey; R, retrospective; P, prospective; M, mean (standard deviation); m, median (range, X–Y); IQR, interquartile range (25–75% percentile).
Proactive: both nutritional (nasogastric tube [NG] or gastrostomy tube [GT]) and respiratory support (non-invasive ventilation [NIV] or tracheostomy with ventilator [TV]).

* The ages of SMA Type III patients in this study ranged from 32 m to 248 m.

[a] SMA Group III defined as maximum motor function attained = walked with aid.

[b] SMA Group III subjects stopped walking by age 14 y (5 of 12 subjects were age >30 y).

[c] SMA Type IIIa defined as first abnormalities obvious <3 y and subjects walked without support.

[d] SMA Type IIIa defined as disease onset <2 y and best function was walk independently. Percentages derived from Kaplan–Meier plot.

upon intensity of care provided and the importance of the number of copies of the *SMN2* gene as a prognostic biomarker. Table 2C summarizes the risk of loss of ambulation in SMA type 3 patients.

To summarize the survival data from the type 1 studies cited here, a few conclusions can be drawn:

1 Earlier age of onset of symptoms is generally associated with shorter survival [25,26]. Infants with type 1B (symptom onset <3 months of age) as a group have shorter survival than those with type 1C (symptom onset 3–6 months of age) [27], but survival is similar when ventilation and nutritional support are provided [28].
2 The number of copies of the *SMN2* gene is a strong predictive biomarker: survival curves for SMA patients with 2 copies have a more rapid and linear decline than do those with 3 copies [25,28–30].
3 The type and extent of supportive care provided prolongs survival, but often due to dependence upon gastrostomy tube for nutritional support and non-invasive ventilation or tracheostomy/ventilator support.
    a. The mean/median age at death is approximately 6/10 months when "palliative", comfort care is provided [31].
    b. "proactive" ventilation support (via non-invasive ventilation [NIV], bi-level positive airway pressure [Bi-PAP] or tracheostomy interfaces) increases survival by months to years [11,27,32–35].
    c. When considering the *combined endpoint* of age at death or age when permanent ventilation was required (defined generally as 16+ hours/day of non-invasive ventilation support for 14+ days, in the absence of an acute reversible illness or post-operatively, or tracheostomy) it becomes clear that increased survival is dependent upon these supportive measures:
        i. A retrospective registry study highlighted the effect of early nutritional and ventilation intervention: those born in 1980–1994 had a median age at death of 8.5 months versus >100 months for those born in 1995–2006 (when supportive care was commonly provided), and for the combined endpoint was 7.5 versus 24 months respectively [8].
        ii. When "reactive" ventilation and nutrition support were variably provided, following the clinical indication for this support, the mean/median age to the combined endpoint was 7.3/6.1 months and for those with 2 copies of the *SMN2* gene was mean/median of 7.8/6.5 months [25].
        iii. A prospective study showed the combined endpoint for those with 2 copies of the *SMN2* gene was a median of 10.5 months [28].

Survival in type 2 patients is now commonly into the 3rd decade and with one study having median survival to beyond age 40 years [36]. Survival for type 3 patients is normal [37].

Recent studies, using motor and developmental assessments, have also explored longitudinal changes in motor function, showing how this continues to decline after diagnosis. At symptom onset type 1 infants generally have reduced motor skills, the majority will have no head control, and new motor skills are never subsequently achieved [38]. Thus, prolonged survival, with nutritional and ventilation support, does not enhance motor development.

Eugenio Mercuri reported data on type 2 and 3 SMA. With improvements in standard of care the overall natural history has improved compared to what was reported until two decades ago

[37]. While early studies report a rapidly progressive loss of motor and respiratory function in type 2 SMA, recent studies suggest that the progression is much slower [39]. If considering one year of follow up, the mean changes in motor or respiratory function are minimal [40] even though a longer follow up will reveal some decline [39]. An international effort has recently been made to define trajectories of progression by using a large dataset combining data from large networks in US, UK and Italy. This effort confirmed that, using the Hammersmith Functional Motor Scale Expanded (HFMSE), the changes over 1 year are minimal but that different trajectories of progression can be identified [38]. Non-ambulant patients tend to improve before reaching the age of 5 years while after this age they will tend to show some decline. In ambulant patients, the profile is slightly different as the decline is more obvious in the years preceding puberty. The patients who showed a more rapid decline were those who developed contractures or severe scoliosis or a sudden increase in weight confirming that some aspects of care are extremely relevant in the progression of the disease.

Francesco Muntoni (UK) reported how in SMA type 2 different standards of care can affect the progression of the disease, reporting the experience of their group on the effect of early monitoring and intervention in different aspects including nutrition, gastrostomy, early scoliosis and management of respiratory infection, on the progression of the disease.

Jes Rahbek reported the experience in a large cohort of type 2 adult patients. Despite the improvement in survival that makes the transition to adulthood and old age not just possible but very likely, the literature on adult type 2 SMA is still limited [41,42]. A recent survey conducted in Denmark suggested that although adult patients are considered to be more stable compared to young prepubertal patients, deterioration in physical function and muscle strength can still occur [43]. The deterioration may affect different aspects. Contractures in shoulders, elbows and wrist extension can increase and tend to be increasingly asymmetrical over time. One major concern is a progressive limitation of mouth opening and more generally, orofacial problems affecting speech and eating that can be found in all age groups but tend to increase over time and can also affect ventilator use. These aspects are often underestimated and not discussed adequately with adult patients and, as suggested by the recent survey, standards of care should be implemented to include recommendations also for them.

2.1.2. Setting the frame: 2. Standards of care and clinical trials

In this session the discussion focused on how SOC has been addressed in SMA clinical trials. Richard Finkel and Enrico Bertini (Italy) reported a review of the existing trials in type 1 and 2 SMA in order to assess if different standards of care had been used to establish inclusion/exclusion criteria or stratification of the existing clinical trials.

In clinical trial for type 1 patients there were often requirements for infants being stable in the weeks before enrollment, and for concordance with the published 2007 standard of care guidelines. Trial criteria have, however, generally lacked specific suggestions on palliative versus proactive care. This is an important point as multicenter studies can be challenged by variability in SOC among the sites and even within the same site some variability is due to the fact that parental autonomy must be maintained. This has been the object of several discussions with ethicists, regulators and advocacy groups trying on one side to allow parental decisions about palliative care, while supporting the participant for sufficient time to respond to drug [44].

In type 2, severe scoliosis or scoliosis surgery, severe contractures, and need for ventilation above 13 hours have been used as exclusion criteria in recent and current studies. No additional specific gastrointestinal/nutrition issues have been considered, apart from generally requiring the patient to be healthy and meet the inclusion criteria of the study. Some studies also suggested that participants should follow the published guidelines on care standard for SMA without going into more details. One study using an AAV9 gene transfer therapy in type 1 SMA did require swallow studies to be performed at the screening visit and if aspiration was identified then supplemental feeding was required for entry into the study. The possibility that new therapies for SMA may improve aspects of care and overall well-being, such as reducing the number of respiratory infections and hospital admissions, was also discussed. Patients with SMA have many co-morbidities which have been identified as adverse events in recent studies. These are potentially amenable to improvement and need to be considered as part of the standard of care of the patient with SMA.

Agata Robertson (UK) reported the results of a recent survey in UK and provided an overview of how TREAT-NMD developed global registries, including data from 24 national registries around the world. This allowed mapping some differences in care standards and to highlight areas of controversies that require further discussion.

2.2. Patient perspective

Anna Wittchen contributed that physician access is difficult for adults with type 2, especially emergent care for adults who may not be able to speak effectively for themselves. Women's issues and pregnancy also need further attention – how to maintain motor and respiratory function during a pregnancy and the need to educate obstetricians on treatment of the pregnant woman with a neuromuscular disorder. Transition from a pediatric to an adult clinic and hospital remains a challenge for many patients and warrants further attention.

Mencia de Lemus highlighted the importance of having guidelines on how to handle emergencies (anesthetics, intubation, oxygen, antibiotics) as this is where patients can be in a more vulnerable situation, and having a consensus about these issues could be life-saving.

2.3. Preliminary results of the individual working groups

2.3.1. Diagnosis and genetics

Francesco Muntoni and Brunhilde Wirth reported on the diagnosis and genetic working group. This included 11 physicians who were involved in various steps of the process.

After a review of the literature, 2 rounds of Delphi analysis were used to identify and rank in order of relevance the role of different diagnostic tests commonly used in SMA, to discuss the relevance of the number of *SMN2* copies and their value in predicting severity of the phenotypes. The questions also investigated possible diagnostic scenarios to use if the *SMN1* gene is not homozygously absent in an individual with features consistent with SMA. The final questions regarded genetic topics that were thought to be important to discuss with SMA patients and their families. There was consensus that genetic testing is the first line investigation when this condition is suspected in a typical case and that muscle biopsy or electromyography should not be performed in a typical presentation. There was also consensus that, at variance with previous recommendations, the current gold standard is *SMN1* deletion/mutation and *SMN2* copy number testing, with a minimal standard of *SMN1* deletion testing. Other areas concerning the value of *SMN2* copy number were more controversial and a further Delphi round was planned to complete the task.

2.3.2. Pulmonary

Anita Simonds and Hank Mayer reported on the pulmonary working group. This included 11 physicians for the medical aspects and one patient and two parents to share their opinion on possible other aspects that the patients/caregivers believed to be important. After a review of the literature, the first round was designed to use open questions to identify the recent biggest advancements in respiratory care and the barriers to providing effective pulmonary care in patients with SMA. Questions were also asked to identify the most important aspects of pulmonary morbidity, the most useful assessments of respiratory function and the most important supportive respiratory therapies in SMA.

The second round, including also patient representatives, aimed at ranking the best aspects of care, monitoring or pulmonary issues. As there seemed to be overlapping opinion, not consensus, a third additional round of questions was sent out to more deeply evaluate the strategies.

Preliminary results were shown for each of these aspects. There were consensus and reasonable data showing that both assisted airway clearance and non-invasive ventilation were helpful in SMA-1 and SMA-2. There was also consensus on when to start both interventions, and initiate NIV but there was less agreement on how to initiate mechanical insufflation-exsufflation for secretion clearance. For type 1 there was consensus based on both literature and expert opinion for the pre-symptomatic initiation of both assisted airway clearance and non-invasive ventilation, i.e. “proactive care” as compared to “reactive care”.

Following discussion, it was agreed that a 4th round of Delphi was needed to complete the task.

2.3.3. Acute management

Mary Schroth reported on the acute management working group. This included 13 physicians. After a review of the literature, the first round was designed to use open questions to identify the most important aspects of acute care. More specifically, the questions investigated the most important concerns when an individual with SMA develops an acute illness, starting from the advice given to families when someone with SMA becomes ill at home and issues regarding transportation to a medical facility. The questions also regarded the most important concerns when someone with SMA is hospitalized and/or requires surgery. The first round of responses provided a large number of possible interventions with some common key themes. This focused upon the need for anticipatory planning between families and care providers for acute illness management, and with the creation of documents such as a check-list or electronic medical record-accessible documents. A second round of Delphi was in progress to rank the open responses obtained in the first round.

2.3.4. Nutrition, growth and bone health

Enrico Bertini and Rebecca Hurst Davis reported on this working group. There were 15 participants. The first Delphi was completed and the second one was pending analysis at the time of the workshop. There are many questions regarding appropriate nutrition for individuals with SMA. This WG sought to expand the nutrition section from the previous consensus statement, which provided information on safe swallowing as well as GI dysmotility. Nutrition affects all individuals with SMA because everybody requires essential nutrients to survive. However, aspects of diet are affected by individual circumstances, specific needs, and degree of intervention desired by the individual and families. Since there are few nutrition studies specifically targeting SMA, experts relied on clinical experience as well as small studies and animal studies to make recommendations. It was acknowledged that there is much more research to be done in this area, but still sought consensus and understanding to define best nutrition practices for individuals with SMA. The literature review supported proactive nutrition support. Also, there are reports of increased glucagonemia in the mouse model and alpha cells in pancreas in type 1 patients and elevated insulin levels in type 2 patients, with risk of both hyper- and hypo-glycemia.

2.3.5. Ethics and palliative care

Simon Woods and Thomas Crawford presented this working group. Dr. Woods summarized the deliberations of the working group, an interdisciplinary group of 11 members, including clinicians, bioethics researchers, parents and patient representatives, and pediatric palliative care specialists. The literature review on this theme indicated that there is a very diverse literature which includes important contributions from clinical, social science and bioethics literature. The clinical literature provided little hard evidence and no consensus regarding standards of palliative care as applied to SMA. The working group was therefore unable to establish a consensus but identified 3 key areas for future analysis: (1) The concept of palliative care as applied to SMA, (2) Patient management and decision-making, (3) Managing expectations.

Although the concept of palliative care has been defined and re-interpreted many times there is a need to regard this as

an ongoing reflexive process especially when applied to contexts, like SMA, that are not static. This should also be reviewed in consideration of the recent advances in SMA therapeutics that have created substantial reason for hope for changes in prognosis.

2.3.6. Physical therapy and rehabilitation

Jacqueline Montes, Elena Mazzone and Marion Main summarized the Physical Therapy and Rehabilitation WG. There were 12 participants: 10 physical therapists, 1 occupational therapist, and 1 physiatrist. Two patients with SMA participated: one adult with type 3, one adolescent with type 2 and one parent of a child with type 1. Three participants from the pharmaceutical industry contributed. A literature review included 5 search terms and 54 papers were reviewed with each characterized for quality. Two rounds of Delphi and four conference calls were conducted prior to the workshop. An impact score was generated and consensus was determined by evaluation of the variance of the ranking scores, with low variance representing a high level of agreement.

Topics important to address in non-sitters include pulmonary function, muscle weakness, postural control and contractures. Clinical evaluations should include administering the CHOP INTEND infant motor scale and assessment of head control and body posture.

For sitters, the main objectives identified for rehabilitation are to prevent contractures and scoliosis, maintain joint mobility, and maintain, restore or promote function and mobility. Clinical evaluations for sitters should include postural control and functional scales, such as the Hammersmith Functional Motor Scale Expanded.

Exercise programs were thought to be most important for walkers. Clinical evaluations for walkers should include administering timed function tests including the six-minute walk test.

The frequency with which rehabilitation services should be minimally provided was difficult to address with limited evidence in the literature, but it was thought to be important to define.

2.3.7. Orthopaedics

Michael Vitale and Brian Snyder presented the Orthopedic WG summary remotely, with contributions by Susana Quijano-Roy at the workshop. There were 13 members in this WG. Results were shared with participants from pharmaceutical companies but not with parents or patients.

Two rounds of Delphi were performed, and included approximately 30 questions within 6 topics. The main topics were:

a. Identification of the optimal timing of spinal instrumentation for correction of scoliosis.
b. Management of contractures: there are no accepted surgical guidelines or indications in the literature for the surgical treatment of joint contractures in SMA.
c. Orthosis. There was divided consensus on the use of a thoracolumbosacral orthoses (TLSO) to specifically prevent progression of scoliosis in skeletally immature patients with SMA.

2.4. Other organ system involvement

Jan Kirschner presented a summary of their activities. There were 16 members in this WG, including participants from pharmaceutical companies and patients.

Two rounds of Delphi were performed. The main topics were related to a possible heart, liver, kidney or brain or metabolic involvement. There was consensus that other organ systems involvement is generally rare in SMA, but probably more common in severely affected patients.

Routine diagnostic testing was not recommended and should rather be based on clinical symptoms. Metabolic monitoring was suggested in non-ambulant patients during illness and/or fasting.

2.5. Medication

Many participants addressed the need to review the use of medications in common use for the management of patients with SMA. It was decided that a separate survey should be conducted following the workshop to address this topic.

2.6. Open discussion

Additional topics that need to be addressed: dental care, care of the pregnant woman with SMA and sexuality.

ENMC SMA Workshop Study Group

E. Bertini (Rome, Italy)
K. Chen (NYC, USA)
T.O. Crawford (Baltimore, USA)
V. Dubowitz (London, UK)
M. de Lemus (Madrid, Spain)
R. Graham (Philadelphia, USA)
R. Hurst Davis (Salt Lake City, USA)
S. Iannaccone (Dallas, USA)
J. Kirschner (Freiburg, Germany)
M. Main (London, UK)
O. Mayer (Philadelphia, USA)
E. Mazzone (Rome, Italy)
J. Montes (NYC, USA)
F. Muntoni (London, UK)
A. Murphy, *parent representative* (UK)
S. Quijano-Roy (Paris, France)
A. Robertson (Newcastle, UK)
M. Schroth (Madison, USA)
A. Simonds (London, UK)
B. Snyder (Philadelphia, USA)
M. Vitale (NYC, USA)
A. Wittchen (Germany)
S. Woods, *patient* (Newcastle, UK)
Y. Qian (NYC, USA)
B. Wirth (Cologne, Germany)

Acknowledgements

This 218th ENMC workshop was made possible thanks to the financial support of the European Neuromuscular Centre (ENMC) and ENMC main sponsors: Association Française

contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Muscular Dystrophy UK, Muskelsvindfonden (Denmark), Prinses Beatrix Spierfonds (The Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Telethon Foundation (Italy), Spierziekten Nederland (The Netherlands) and Associated members: Finnish Neuromuscular Association (Finland). We are grateful to the LGMD2I research Fund and Cure CMD for their generous support to this workshop.

We are very grateful for financial support and workshop initiating efforts from SMA Support UK, and for financial support from Cure SMA and SMA Foundation. The role of TREAT NMD in coordinating the working groups and in facilitating the meeting is also acknowledged.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.02.014.

References

[1] Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet 2012;20:27–32.

[2] Dubowitz V. Muscle disorders in childhood. 2nd ed. London: W. B. Saunders; 1995.

[3] Dubowitz V. Chaos in the classification of SMA: a possible resolution. Neuromuscul Disord 1995;5:3–5.

[4] Finkel R, Bertini E, Muntoni F, Mercuri E. 209th ENMC international workshop: outcome measures and clinical trial readiness in spinal muscular atrophy 7–9 November 2014, Heemskerk, The Netherlands. Neuromuscul Disord 2015;25:593–602.

[5] Hirtz D, Iannaccone S, Heemskerk J, Gwinn-Hardy K, Moxley R 3rd, Rowland LP. Challenges and opportunities in clinical trials for spinal muscular atrophy. Neurology 2005;65:1352–7.

[6] Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol 2007;22:1027–49.

[7] Delbecq AL, Van de Ven A, Gustafson DH. Group techniques for program planning: a guide to nominal group and Delphi processes. Management applications series. Scott Foresman; 1975.

[8] Oskoui M, Levy G, Garland CJ, Gray JM, O'Hagen J, De Vivo DC, et al. The changing natural history of spinal muscular atrophy type 1. Neurology 2007;69:1931–6.

[9] Messina S, Pane M, De Rose P, Vasta I, Sorleti D, Aloysius A, et al. Feeding problems and malnutrition in spinal muscular atrophy type II. Neuromuscul Disord 2008;18:389–93.

[10] Ramelli GP, Aloysius A, King C, Davis T, Muntoni F. Gastrostomy placement in paediatric patients with neuromuscular disorders: indications and outcome. Dev Med Child Neurol 2007;49:367–71.

[11] Mannaa MM, Kalra M, Wong B, Cohen AP, Amin RS. Survival probabilities of patients with childhood spinal muscle atrophy. J Clin Neuromuscul Dis 2009;10:85–9.

[12] Chandran S, McCarthy J, Noonan K, Mann D, Nemeth B, Guiliani T. Early treatment of scoliosis with growing rods in children with severe spinal muscular atrophy: a preliminary report. J Pediatr Orthop 2011;31:450–4.

[13] Sponseller PD, Yang JS, Thompson GH, McCarthy RE, Emans JB, Skaggs DL, et al. Pelvic fixation of growing rods: comparison of constructs. Spine 2009;34:1706–10.

[14] Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. Arch Dis Child 2011;96:426–32.

[15] American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics 2004;114:874–7.

[16] Darras BT, Finkel RS. Natural history of SMA. In: Sumner CJ, Paushkin S, Ko C-P, editors. Spinal muscular atrophy: disease mechanisms and therapy. 1st ed. Elsevier, Academic Press; 2016 [Chapter 25].

[17] Brandt S. Course and symptoms of progressive infantile muscular atrophy; a follow-up study of 112 cases in Denmark. *Arch Neurol Psychiatry* 1950;63:218–28.

[18] Byers RK, Banker BQ. Infantile muscular atrophy. *Arch Neurol* 1961;5:140–64.

[19] Pearn JH, Wilson J. Acute Werdnig-Hoffmann disease: acute infantile spinal muscular atrophy. *Arch Dis Child* 1973;48:425–30.

[20] Thomas NH, Dubowitz V. The natural history of type I (severe) spinal muscular atrophy. *Neuromuscul Disord* 1994;4:497–502.

[21] Ignatius J. The natural history of severe spinal muscular atrophy–further evidence for clinical subtypes. *Neuromuscul Disord* 1994;4:527–8.

[22] Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol* 1995;52:518–23.

[23] Borkowska J, Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, Zerres K. Early infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease) with prolonged survival. *Folia Neuropathol* 2002;40:19–26.

[24] Lemoine TJ, Swoboda KJ, Bratton SL, Holubkov R, Mundorff M, Srivastava R. Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? *Pediatr Crit Care Med* 2012;13:e161–5.

[25] Rudnik-Schoneborn S, Berg C, Zerres K, Betzler C, Grimm T, Eggermann T, et al. Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type I in Germany: implications for clinical trials and genetic counselling. Clin Genet 2009;76:168–78.

[26] Ge X, Bai J, Lu Y, Qu Y, Song F. The natural history of infant spinal muscular atrophy in China: a study of 237 patients. J Child Neurol 2012;27:471–7.

[27] Ioos C, Leclair-Richard D, Mrad S, Barois A, Estournet-Mathiaud B. Respiratory capacity course in patients with infantile spinal muscular atrophy. Chest 2004;126:831–7.

[28] Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology 2014;83:810–17.

[29] Petit F, Cuisset JM, Rouaix-Emery N, Cancés C, Sablonnière B, Bieth E, et al. Insights into genotype-phenotype correlations in spinal muscular atrophy: a retrospective study of 103 patients. Muscle Nerve 2011;43:26–30.

[30] Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358–68.

[31] Cobben JM, Lemmink HH, Snoeck I, Barth PA, van der Lee JH, de Visser M. Survival in SMA type I: a prospective analysis of 34 consecutive cases. Neuromuscul Disord 2008;18:541–4.

[32] Chung BH, Wong VC, Ip P. Spinal muscular atrophy: survival pattern and functional status. Pediatrics 2004;114:e548–53.

[33] Barois A, Mayer M, Desguerre I, et al. [Spinal muscular atrophy. A 4-year prospective, multicenter, longitudinal study (168 cases)]. Bull Acad Natl Med 2005;189:1181–98.

[34] Bach JR, Saltstein K, Sinquee D, Weaver B, Komaroff E. Long-term survival in Werdnig-Hoffmann disease. Am J Phys Med Rehabil 2007;86:339–45.

[35] Park HB, Lee SM, Lee JS, et al. Survival analysis of spinal muscular atrophy type I. Korean J Pediatr 2010;53:965–70.

[36] Farrar MA, Vucic S, Johnston HM, du Sart D, Kiernan MC. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. J Pediatr Orthop 2013;162:155–9.

[37] Zerres K, Rudnik-Schoneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci 1997;146:67–72.

[38] Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromuscul Disord 2016;26:126–31.
[39] Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology 2012;79:1889–97.
[40] Kaufmann P, McDermott MP, Darras BT, Finkel R, Kang P, Oskoui M, et al. Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year. Arch Neurol 2011;68:779–86.
[41] Werlauff U, Steffensen BF, Bertelsen S, Floytrup I, Kristensen B, Werge B. Physical characteristics and applicability of standard assessment methods in a total population of spinal muscular atrophy type II patients. Neuromuscul Disord 2010;20:34–43.
[42] Werlauff U, Fynbo Steffensen B. The applicability of four clinical methods to evaluate arm and hand function in all stages of spinal muscular atrophy type II. Disabil Rehabil 2014;36:2120–6.
[43] Jeppesen J, Madsen A, Marquardt J, Rahbek J. Living and ageing with spinal muscular atrophy type 2: observations among an unexplored patient population. Dev Neurorehabil 2010;13:10–18.
[44] Finkel RS, Bishop KM, Nelson RM. Spinal muscular atrophy type I. J Child Neurol 2017;32:155–60.