Title

Feeding difficulties in children and adolescents with spinal muscular atrophy type 2

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Abstract

Disease course of feeding difficulties in spinal muscular atrophy type 2 is not well documented. Disease-modifying therapies rapidly change the trajectory of motor function and survival in spinal muscular atrophy, but effects on co-morbidities like bulbar function are unknown.

We analysed data concerning feeding problems and their standard of care treatment in 146 patients with spinal muscular atrophy type 2. Data were collected from two separate cohorts: one single-centre retrospective chart review study from the United Kingdom (London), and one prospective questionnaire-based multicentre study from Italy. Cumulatively feeding difficulties were present in 88 patients (60%) in these 2 cohorts. Median age at onset of problems was 6.5years (range 0-16.5 years). Eighty-two patients (60%) showed periods of underweight according to age adjusted body mass index, and thirty-six patients (25%) showed malnourishment with a significant drop on their weight curves. Enteral feeding was indicated in 23 out of 72 patients in the UK cohort (32%) because of weight loss, oropharyngeal dysphagia or aspiration. Gastrostomy and its placement was generally well tolerated, uncomplicated in 96%, never reversed and performed without Nissen fundoplication in 66% of patients. After gastrostomy chest infections improved in 80% and nutritional status (e.g., Body Mass Index) in 84% of patients. These results show that feeding difficulties are a common problem in spinal muscular atrophy type 2. Treatment strategies should be tailor-made on the symptoms and needs of the individual patient.

KEY WORDS

Spinal muscular atrophy, SMA, feeding difficulties, nutrition, underweight

ABBREVIATIONS

SMA= Spinal muscular atrophy

BMI= Body mass index

BMD= Bone mineral density

BMAD= Bone mineral apparent density

DEXA= Dual-energy X-ray absorptiometry

1. Introduction

Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder caused by a homozygous deletion of the *SMN1* gene, or rarely by compound heterozygosity with smaller *SMN1* mutations [1]. SMA is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord. SMA is classified into four different subtypes (types 1-4) based on the highest achieved motor milestone [2]. The most prominent feature of SMA is the deterioration of muscle strength, which affects the axial and limb muscles. The severity of muscle weakness varies significantly between patients resulting in different motor milestone achievement, time to lose these abilities and overall progression rate of disease [2-4].
Scoliosis and respiratory problems result from progressive weakness of paraspinal and respiratory muscles and are common comorbidities in the more severe forms of SMA [5, 6]. Weakness of bulbar muscles and of muscles of the gastrointestinal tract have also been described [7-9]. Feeding difficulties, including swallowing problems and aspiration, chewing problems and over- and underweight, have been reported frequently in SMA type 1 [10-14], to a lesser extent in SMA type 2 [7, 9, 11, 14-18], and sporadically in SMA type 3 [11, 15-18]. Only a limited number of studies have investigated the prevalence of feeding difficulties in SMA type 2 (Table 1).

Guidelines for the standard of care in patients with SMA recommend monitoring of feeding problems including swallowing function and growth parameters, especially in non-sitters [23]. Monitoring in sitters and walkers is suggested, but the prevalence and extent of feeding problems, disease course and complications of feeding

difficulties have not been the focus of recent reports, are poorly characterised and typically reflect the experience of single centres [15, 16, 24, 25].

The two major complications from feeding difficulties are aspiration pneumonia and malnutrition. Swallowing difficulties are an important contributor to pulmonary complications with silent aspiration often unrecognized and underestimated [2, 26]. Periods of (severe) weight loss and chronic under- or overweight are a well-known problem in children and adolescents with SMA [11, 18, 27, 28]. An altered balance between fat mass and fat-free body mass makes interpretation of the standard growth chart references and (age-adjusted) body mass index (BMI) difficult, thus complicating nutritional considerations and recommendations in children with SMA [27].

The development and implementation of disease modifying therapies, like the antisense oligonucleotide nusinersen or gene replacement therapy [29, 30], have shown to change the disease course of motor function and survival in the majority of children with SMA [29, 31-33]. The effects of these innovative and emerging therapies on non-motor co-morbidities are unknown [29, 31, 33, 34]. In the long run, improvement of gross motor abilities alone will not be entirely satisfactory, and improvement of co-morbidities, including bulbar dysfunction, is essential to ensure optimal quality of life. There is therefore an urgent need to collect natural history data on all co-morbidities, motor- and non-motor complications, to evaluate the effects of *SMN*-modulating therapies in these specific areas.

We performed an observational study on feeding difficulties in *SMN*-targeting-treatment-naïve children and adolescents with SMA type 2 in order to evaluate the presence of feeding problems in this particular group of patients. Data were collected from a single-centre retrospective study in the United Kingdom (UK) and a

prospective, multi-centre study in Italy. Additionally, the comprehensive dataset on 72 SMA patients with extensive follow up from the UK cohort allowed a deeper phenotyping and included analysis of the trajectories of the feeding difficulties.

2. Patients and method

2.1 Patients

All participants and/or their legal representatives have given written informed consent. Local Medical Ethical Committees approved both study protocols (protocol numbers: 11DN15; 7/16 and 37/2016).

We used age at onset and acquired motor skills to define SMA types according to the diagnostic criteria defined by the SMA Consortium [2]. Patients with SMA type 2 had an onset between the age of 6 and 18 months and achieved the independent sitting position. In case of discrepancy between age at onset and reached motor milestones, the latter determined the final diagnosis. Patients were subdivided in types 2a and 2b, based on the additional (in)ability to stand and/or walk with support [4].

Feeding difficulties were defined as any trouble with one or more of the following aspects, including eating, chewing or swallowing (including aspiration), prolonged mealtimes or presence of underweight. Prolonged mealtime duration was defined as a mealtime ≥30 minutes, irrespective of age [16, 20].

Two questionnaires were used assessing feeding problems in the UK and Italian cohorts, respectively (Supplementary files S1 and S2). Although both questionnaires

contained different questions on feeding-related problems (e.g. motor function, constipation), items about feeding (meal-time and chewing), swallowing (difficulty swallowing and gastro-oesophageal reflux) and interventions (nasogastric tube, gastrostomy or Nissen fundoplication) were interchangeable and were used in the comparative analyses.

Data on motor function (e.g. highest achieved motor milestones, loss of motor abilities, current motor function), respiratory function, spine curvature and scoliosis surgery status were retrospectively collected from systematic questionnaires used in clinic. Evaluation of motor function (e.g. Hammersmith Functional Motor scale – expanded and revised, Revised Upper Limb Module, Gross Motor Function Measures, MRC scores, loss of motor milestones) was performed in each patient during their follow-up visits. However, in view of the retrospective nature of this study over a long period of time, different functional outcome measures were studied. Motor functional scales could therefore not be used in the analyses as a correlate of feeding problems.

Standard growth charts for height and weight were used as reference (https://www.who.int/growthref/who2007; https://www.cdc.gov). Age adjusted body mass index (BMI) and percentiles were calculated using the Center for Disease and Prevention Children's BMI Tool (https://www.cdc.gov) and WHO reference curves (https://www.who.int/growthref/who2007_bmi_for_age/en/). Underweight was defined as a period of at least 6 months with an age-adjusted BMI <5th percentile[35]. Overweight was defined as a period of at least 6 months with an age-adjusted BMI >85th percentile[35]. Severe weight loss was defined as a drop across 2 or more centile spaces from the individual growth percentile. Using the CDC and WHO

references, only three out of 146 children (2%) showed a discrepancy in BMI percentile classification (e.g. underweight, overweight, normal weight) for one period during follow up. If discrepancies in weight category occurred between the CDC or WHO method, the WHO references defined the final BMI percentile score and classification.

Chest infections included reports of lower respiratory tract infection or pneumonia. Clinical assessments varied in follow up time and therefore periods in survival analysis were adjusted not more than 6 months in order to compress data into time periods.

SMN1 deletion, and if possible *SMN2* copy number status, was determined by PCR or MLPA in certified laboratories in diagnostic setting.

2.1.1 Retrospective chart review cohort (UK)

Data was collected using a retrospective chart review design. All patients were under the care and follow up of the Paediatric Neuromuscular team at Great Ormond Street Hospital London, United Kingdom, in the period from 2008-2018. Clinical care was performed according to the applicable standards of care of that period of time [23, 26]. All patients were systematically assessed during clinic using the SMArtNet or SMA REACH UK forms (SMArtNet Clinical Network/ SMA Research and Clinical Hub, https://clinicaltrials.gov/ct2/show/NCT03520179), including questions on feeding problems (Supplementary file S1). All children reporting swallowing problems (e.g. difficulties swallowing, aspiration, coughing after swallowing, recurrent pneumonia) were further assessed with videofluoroscopy.

Height was measured using arm span. Bone health was evaluated with Dual-energy X-ray absorptiometry (DEXA). Bone mineral density (BMD) and bone mineral apparent density (BMAD) were used to reflect bone density. BMAD was calculated using a transformation of bone area to estimate the volume of each individual vertebra (L1 to L4) to approximate the effects of bone depth and body size [36]. Z-scores (i.e., the number of standard deviations that a patient's BM(A)D differs from the average of a healthy control population of the same ethnicity, sex and age) of BMD and BMAD were calculated and collected as reported by the radiology department in diagnostic setting.

2.1.2 Prospective chart review cohort (Italy)

Data were collected from a prospective multicentre study on nutritional status in children with SMA type 2. Children were recruited from 2015-2018 from two clinical SMA referral centres in Milan (Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta and SAPRE-UONPIA, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico). Clinical care was performed according to the applicable standards of care of that period of time [23, 26].

Data on feeding problems were prospectively collected at the International Center for the Assessment of Nutritional Status (ICANS), University of Milan. Parents of patients filled in an internet-based specific questionnaire on feeding problems [37] (Supplementary file S2). The items in the questionnaire were validated by face-to-face interview about feeding problems. In case of reported problems on swallowing (e.g. difficulties swallowing, aspiration, coughing after swallowing, recurrent pneumonia), children were assessed with a feeding and swallowing observation by a speech and language therapist (SaLT). Videofluoroscopy was indicated if swallowing

problems did not improve after instructions by the SaLT.

Recumbent length was measured using segmental measurements [38].

2.2 Statistical analysis

We used descriptive analysis to present the patient-related characteristics.

Univariate and multivariate tests including dichotomous data were performed using chi-square and/or logistic regression with correction for covariates.

Lifetime probability on predefined symptoms (e.g. feeding problems, gastrostomy) was analysed using Kaplan-Meier survival curves. To detect differences in lifetime probabilities between cohorts, we used the log-rank test. To analyse the presence of a trend of increasing age at time of developing symptoms with milder SMA phenotypes, the Jonckheere-Terpstra test was used.

We analysed effect of SMA type (e.g. 2a or 2b), age, ventilation status, scoliosis surgery and timing of (non-) invasive ventilation (NIV), scoliosis surgery and weight status (e.g. underweight) on the presence and timing of feeding problems by means of Cox regression. Cox regression was only performed in the UK cohort, because of varying follow up time between patients. Age at time of starting respiratory support or/and spinal surgery were incorporated as a time-dependent covariant.

Comparisons between the UK and Italian cohorts were done with Mann-Whitney U or Chi-square tests. We analysed weight, height and BMI differences between the two cohorts per gender and age group using the Mann-Whitney U test. Age groups were defined as follows (female vs male): 1-3.9 years (n=131 vs 92), 4.0-6.9 years (n=155 vs 122), 7-9.9 years (n=123 vs 74), 10.0-11.9 years (n=45 vs 38), 12.0-14.9 years (n=37 vs 26), >15years (n=28 vs 21).

A *p*-value of <0.05 was considered to be significant.

3. Results

We included 146 patients with SMA type 2. Patient' characteristics are presented in Table 2.

SMN2 copy number was available in 28 children.

3.1 Feeding difficulties

Feeding problems were reported in 60% of patients with SMA type 2 (Table 3). Different types of feeding problems (e.g. choking, chewing problems, swallowing problems, aspiration, prolonged mealtime or weight loss) were evenly present among patients. Fifty-seven percent of patients reported more than one problem. Median age at onset of feeding problems was 6.5 years (range 0-16.5 years). Patients with SMA type 2a were more often affected by feeding problems (X^2 $p<0.01$). The age at onset of these problems was not influenced by SMA 2 subtype (MW $p=0.29$).

Clinical assessment of feeding and swallowing by SaLT was done in 57 patients (81%), resulting in advice on posture and food texture leading to improvement of symptoms. Videofluoroscopy was performed in 21 patients who reported swallowing problems. In 17 out of 21 patients the videofluoroscopy showed moderate to severe oropharyngeal dysphagia which lead to the recommendation or initiation of enteral tube feeding. In five patients the clinical signs of aspiration (e.g. recurrent aspiration pneumonia, aspiration in clinic) resulted in enteral tube feeding without confirmation of swallowing disturbances by videofluoroscopy.

Growth curves were collected in all patients (Figure 1). Mean weight was higher in the UK cohort in the age group 1-3.9 years (MW p <0.01), but weight and height did not differ between cohorts in any of the other age groups (all p>0.5).

Height curves followed the reference growth charts in the majority of children up till the age of ten years. Increment in height and weight seemed to slow down faster than the general growth curves after the age of 10 years. Data regarding puberty onset was not available to compare with the slopes of the growth charts.

Thirty-two patients (24%) had a normal weight according to age-adjusted BMI during their whole follow up (Table 3). Eighty-two patients (60%) showed periods of underweight. Thirty-six patients (25%) showed a significant decline in their weight curves at some point during follow up (e.g. dropping from growth percentile curve). Periods of overweight were present in 12% of patients (n=16).

3.2 Deep phenotyping of feeding problems and nutritional status

3.2.1 Feeding difficulties

Additional data on feeding problems and nutritional status were available and were studied in more detail in 72 patients from the UK cohort (Table 3). Median follow up time was 6 years (range 0-16), covering age ranges from 1 to 19 years old.

Feeding problems were present in 35 patients (49%); these included swallowing difficulties and/or aspiration (40%), long meal times (11%), or weight problems (35%) (including periods of under- (60%) or overweight (20%)). Fourteen percent of patients reported a combination of different problems.

Feeding problems were more frequent in SMA type 2a compared to SMA type 2b (32 vs 3; p<0.01). Onset of feeding difficulties correlated with SMA subtype (hazard 2.6; p=0.02) and the age at time of start of non-invasive ventilation (hazard -0.03;

p=0.01), but not with gender, presence of respiratory support, vital capacity at time of feeding problems, presence of scoliosis surgery or age at time of fixation (all p>0.05).

3.2.2 Feeding difficulties and interventions

All seventeen patients clinically suspected of having an unsafe swallowing, had this confirmed on videofluoroscopy and were started enteral tube feeding. In six patients, enteral tube feeding was also indicated because of severe underweight or weight loss (n=5) or severe gastro-oesophageal reflux disease (GORD) (n=1).

In 11 patients nasogastric tube (NGT) was placed for unsafe swallowing (median age 4 years, range 1.0-16.7 years). In ten out of the eleven patients the NGT was converted to gastrostomy. Median age at time of gastrostomy was 8 years (range 2.8 – 18.7 years).

Prevalence of gastrostomy was different between SMA type 2a and 2b (X^2 $p<0.05$). Age at time of gastrostomy did not differ between SMA types (MW p=0.45). Timing of gastrostomy was not predicted by any of the covariates (all p>0.05). In the two patients with SMA type 2b, the gastrostomy was indicated because of static weight and weight loss respectively.

At last follow-up, 4 gastrostomies had not yet been performed, although recommended, and no follow up data was available in these cases while writing this paper. Gastrostomy was generally well tolerated. Only one gastrostomy was complicated with post-operative sepsis. None of the gastrostomies were reversed. Nissen fundoplication was indicated due to the severe gastroesophageal reflux in seven patients (30%) and had been performed at the same time as the gastrostomy.

In only one patient the fundoplication became necessary due to worsening of the gastroesophageal reflux following the gastrostomy.

Fifteen out of 23 patients reporting recurrent chest infections, albeit being on NIV in 7 patients, received a gastrostomy. Twelve patients (80%) reported no chest infections after placement.

BMI improved in 16 out of 19 children (84%) after gastrostomy (Figure 2).

3.2.2 Nutrition and bone health

Vitamin D supplementation was prescribed in 59 patients (79%). Treatment periods with vitamin D varied per patient (e.g. temporary supplementation or chronic treatment), but the majority (85%) received chronic treatment once they had started.

Vitamin D levels were measured in 21 patients before treatment (mean level 74nmol/L (range 21 to 158)). During follow up 28% of patients (n=17) showed a vitamin D deficiency <75nmol/L despite routine treatment and received additional dosing.

Routine DEXA scan analysis was performed in 27 patients (37%). In fifteen children follow up scans were available (mean follow up time between scans 1.7 years; range 0.75 to 7 years). Median BMD Z-scores were -3.75 (-0.8 to 5.50) and median BMAD Z-scores adjusted for age were -2.84 (range -0.5 to -5.23).

Seven children (10%) started bisphosphonate treatment because of low DEXA scores and/or fractures. Median BMAD-Z scores were -4.3 before treatment (range -0.8 to -6.3; BMAD score unknown in one child due to severe contractures).

3.3 Comparative analysis of the UK and Italian cohorts

We compared the prevalence and treatment of feeding problems between the UK and Italian cohorts (Table 2). Although the number of patients on NIV did not differ between the two cohorts, the age at start of NIV was lower in the Italian cohort; this is possibly related to a pro-active protocol, which includes starting of prophylactic NIV.

Subjective exploration on feeding problems was done by a structured questionnaire in both cohorts. Feeding problems were more often reported in the Italian cohort (80% versus 49%; $p<0.01$). The prevalence and probability of reporting feeding problems was different between the two cohorts (log rank $p<0.01$; X^2 $p=0.01$). Age at start of feeding problems did not differ with a median age of six years (MW $p>0.05$). In the UK cohort, all 17 patients suspected of swallowing difficulties were assessed with videofluoroscopy. In the Italian cohort, all 40 patients with suspected swallowing problems received clinical review and advice on how to address their swallowing difficulties; in only 10% of patients (n=4) a videofluoroscopy was performed. Invasive interventions, e.g. enteral feeding by NGT or gastrostomy, were only initiated in the UK cohort. Ten patients (43%) in the UK cohort were >10years of age when nasogastric tube (NGT) or gastrostomy was placed, and the median age at last follow up in the Italian cohort was of 7 years (1-16).

4. Discussion

Feeding difficulties are frequently described in SMA type 1, but less often investigated in the milder SMA type 2. We showed that feeding difficulties are a common problem in patients with SMA type 2. Self-reported feeding difficulties including swallowing problems, aspiration, chewing and choking problems, weight loss and prolonged mealtime, were present in 60% of our 146 patients. SMA severity reflected by subtype and the age at need of respiratory support were associated with the presence of feeding problems. Underweight or severe weight loss were significant problems in SMA type 2, in 60% and 25% of patients respectively, with enteral feeding required in 16%.

Studies on natural history of SMA are often limited to motor strength and function and few studies have investigated feeding problems in SMA type 2 [7-9, 15-17, 20, 21, 39]. Prevalence rates of reported feeding issues vary extensively ranging from 20-75%. This is probably the result of varying definitions of feeding problems (e.g. dysphagia, choking, chewing, limited mouth opening, weight problems or a combination of different problems), detection (e.g. questionnaires, swallow observations, videofluoroscopy) and study methods (e.g. retrospective, prospective) [7-9, 15-17, 20, 21, 39].

In our study, gastrostomy rate was high in the UK cohort (32%) and was recommended for swallowing as well as weight gain problems. In this cohort of patients, gastrostomies were associated with positive outcomes with improvement of aspiration (80%), reduction of respiratory infections (80%) and weight control (84%). Importantly, the majority of the procedures were performed without Nissen fundoplication. The recent standard of care document does not provide a definitive

consensus on whether gastrostomies should always be combined with Nissen fundoplication in patients with SMA, as different units have different practices [23]. In the UK centre the Nissen fundoplication is only considered in case of demonstrated severe gastroesophageal reflux and importantly the gastrostomy without fundoplication was successful in 70% of patients, with only one patient requiring a subsequent Nissen fundoplication [23]. Another crucial finding from our study is the altered respiratory function, e.g. decrease in the number of (silent aspiration) pneumonias or airway tract infections, after gastrostomies in 80% of patients with these pre-existing comorbidities. Although some of the patients also received NIV during follow up, in at least 55% the improvement of respiratory complications could clearly be attributed to the gastrostomy. The improvement of aspiration-related respiratory complications after gastrostomy reflects the importance of proactive strategies on feeding problems [23].

The high prevalence of feeding problems should prompt awareness for these problems in all patients with SMA type 2, especially in the phase of declining strength or pulmonary function.[16] Feeding difficulties reflect the different stages of eating or drinking and their involvement of various systems to carry out these functions, including bulbar and spinal motor neurons, muscles and neuromuscular junction. All of these systems are more or less affected by SMN deficiency in SMA. Weakness, fatigability and contractures or postural changes result in problems with either the pre-oral [7, 17], oral [8], and/or pharyngeal phase [20]. Our correlation with timing of NIV and the onset of feeding difficulties implicates the importance of strength and posture of trunk muscles in the development of feeding problems.

Standardized, repeated questionnaires are able to detect specific problems in feeding, and will raise awareness in patients, parents and caregivers in recognizing these problems. However, the relatively slowly progressive course of SMA type 2 including its bulbar problems is prone to mask the recognition of symptoms by adaptations and strategies, even when patients are specifically questioned. The assessment of feeding problems is complicated by the lack of validated objective measures that ideally can analyse all potential problems in one assessment (e.g. videofluoroscopy [40], ultrasonography [41] or EMG [20]). Current practice guidelines suggest additional analysis and monitoring with videofluoroscopy in case of a positive history of feeding problems or feeding evaluation in patients with SMA type 2 [23]. The data of the UK cohort indicate a high rate of pathological videofluoroscopies once a dysfunction was clinically suspected. The abnormal videofluoroscopy was often a trigger to consider the gastrostomy insertion.

Feeding difficulties (e.g. problems with food intake) are not be confused with nutritional intake and status (e.g. problems with food or nutrition quality), although both are inevitably connected. Malnourishment or compromised nutritional status is frequently present in SMA type 2 [11, 42]. In our cohort 60% was underweight, while 12% was overweight according to BMI during some period of time at follow up. BMI has proven to be unreliable in SMA and might overestimate body composition at both ends of the spectrum, because of the misinterpretation of body fat and fat-free mass [14, 38]. At least in 25% of cases in our cohort malnourishment was reflected by significant decline of weight, e.g. drop from the growth percentile. Decline in weight or change from growth percentile is not influenced by the sort of reference or

type of measurement and is therefore a robust and clear sign of nutritional failure that should trigger intervention.

The lack of SMA specific growth curves and dietary guidelines complicates the care for patients with SMA. We used general growth curves for height and weight observation as no other SMA-specific references are available. We observed a flattening slope in height and weight above the age of ten in males and females, which might reflect an SMA specific growth pattern. Similar growth patterns are seen in children with premature puberty after their growth spurt [43, 44] or might be the result of an alternative method of measuring height. Height measurement by arm span slightly underestimates height in healthy children, especially >10 years of age [45, 46], but overall there is fairly good correlation. Arm span growth curves in neuromuscular disorders are only systematically analysed in Duchenne Muscular Dystrophy (DMD) [47]. The reliability in patients with SMA has not been investigated before and could be different from DMD because of a different pattern of weakness and contractures.

Nutritional interventions should ideally include individualized dietary, supplement and caloric intake, adjusted to the body composition, bone health and caloric need based on movement abilities, daily exercise and whether or not respiratory support is used. Baranello et al. previously stressed the importance of bone health management in patients with SMA types 2 and 3 [48]. The current clinical guideline recommends yearly evaluation with vitamin D levels and DEXA in order to anticipate on osteoporosis or osteopenia [23]. Our findings of low bone density resulting in (subclinical) fractures and/or osteoporosis in 10% of children and vitamin D deficiency in 30% of children, although not investigated systematically, underline those recommendations.

A limitation of this study is the fact that data were collected from two centres with two different protocols (retrospective versus prospective) with the intrinsic risk of including a heterogeneous population with over- and underestimation of symptoms. Furthermore, the different in the interventions, and specifically in the insertion of gastrostomies, likely reflect differences in the interpretation and implementation of the standards of care and on the approach to feeding difficulties between different cultures, during a prolonged follow up period where an overlap between two different guidelines of standard of care might have occurred [23, 26]. Although it is more likely that the longer follow up and older age at last assessment in the UK cohort may have contributed to the differences in intervention rate (e.g NG tubes, gastrostomies) between the two cohorts, differences in dietary interventions (e.g. energy drinks, caloric intake, supplements) with the Italian cohort receiving more proactive caloric supplementation could also have resulted in less underweight patients with a lesser need for invasive interventions. We also note that in the Italian cohort there was more frequently an earlier, preventive use of nocturnal ventilatory support. We cannot exclude that this could have contributed to the differences observed.

In addition, differences in the cultural approach and application of standards of care protocols for the management of feeding difficulties in SMA patients cannot be excluded.

In our opinion, the data from the Italian cohort may be representative of the different approach and management of feeding difficulties and undernutrition in southern and eastern European countries. In Mediterranean countries, caregivers are much less receptive to enteral feeding and invasive interventions like gastrostomy and NG tube

placement, compared to Northern European countries, including the UK, where these approaches are more acceptable from a cultural perspective. Large regional differences could potentially be found even when comparing North America to Europe, with a higher incidence of G-tube placement in North America [25].

These real-world findings underline the importance of recognizing differences between centres and countries, and the implications that these differences could play in multicentric studies, especially in the case of the milder and more chronic forms of SMA where guidelines are less stringent and assessments and interventions are based on the clinical evaluation of the treating physician.
When trying to identify the reasons for the different incidence of reports on feeding problems in the 2 cohorts, we identified a few possible explanations. First, the study methods differed. Prospective studies are prone to overestimate, while retrospective studies tend to underestimate prevalence's due to reporting and awareness bias. In addition, the duration of follow up was longer in the UK cohort and the two cohorts differed in SMA severity based on the percentage of SMA type 2a patients, mean age at inclusion and number of scoliosis surgical interventions. However, age at onset and types of feeding problems were similar in both cohorts and provide a good reflection of these comorbidities in patients with SMA type 2. Unfortunately, we were not able to correlate the presence of feeding problems or the effects of treatment strategies with motor function, since data on motor scales or muscle strength evolved during the study period and was not prospectively defined.

In conclusion, wide variety of feeding problems are common in children and adolescents with SMA type 2 at any age and disease stage. Recommendations and

interventions concerning nutrition, scoliosis and respiratory care might differ according to country-specific protocols and health care systems and cultural backgrounds [25]; nevertheless the updated standard of care recommendations aim to improve patient's care and treatment comparability between centres [23, 49, 50]. Our study provides further indications of areas in which future research will be of help and on the importance to standardise the assessment and intervention in large multicentre cohort studies of SMA patients.

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Figure legends

Legend Figure 1AB Growth charts in children and adolescents with SMA type 2

*Growth charts of 146 children and adolescents with SMA type 2. A) Growth charts for height for age in females and males. From the age of 10 years, curves slow down compared to normal values. B) Growth charts for weight for age in females and males. Greys line represent 5th, 50th and 95th percentile curves from reference charts (*https://www.cdc.gov*).*

Legend Figure 2. Body mass index in relation to timing of gastrostomy in UK cohort

Trajectories of age-adjusted body mass index (BMI) in 19 patients from the UK cohort. All patients received gastrostomy during follow up. Each individual line reflects age-adjusted BMI over time per patient. Time until and after gastrostomy is shown at x-axis with time point '0' reflecting the moment of gastrostomy. In 16 out of 19 patients age-adjusted BMI improved after gastrostomy placement, although 8 were still severely underweight (age-adjusted BMI <5th percentile).

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