Dysphagia in patients with spinal muscular atrophy

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Dysphagia in patients with spinal muscular atrophy

Dysfagie bij patiënten met spinale musculaire atrofie
(met een samenvatting in het Nederlands)

Proefschrift

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Contents

Chapter 1

General introduction

Neuromuscular disorders (NMDs) are chronic diseases that have a major influence on the lives of patients and their families (1-3). Estimates are that in the Netherlands up to one in 80 people suffers from an NMD (4). More than 600 (mostly rare) types of NMD can be distinguished, many of which are genetic in origin. Based on the anatomical location of the disorder, NMDs can be categorized as 1) diseases of the muscle; 2) neuromuscular junction disorders; 3) nerve root, plexus or peripheral nerve disorders; 4) (lower) motor neuron diseases (5, 6). Symptoms show a high variability between and within NMDs, but the main features are progressive muscle weakness, loss of muscle mass and unusual muscular fatigue. This may lead to a variety of symptoms, including dysphagia, defined as 'a swallowing disorder, involving the oral cavity, pharynx, oesophagus or the junction between the distal oesophagus and proximal stomach' (7)*.

Dysphagia refers to a disruption of the swallowing process (i.e. sucking, swallowing and mastication), that compromises safety, efficiency and adequacy of nutrient intake. It affects mealtime participation because it takes more time and effort to ingest food and liquid; swallowing may even be impossible. Dysphagia can have a far-reaching impact on the affected person, as it can cause malnutrition and dehydration, general health problems, chronic lung disease and weight loss (8, 9). It can lead to decreased social participation and has a negative impact on the quality of life. It is estimated that 47% of the children and 36% of the adults with NMD, have some form of dysphagia (10, 11).

One of the most common hereditary neuromuscular diseases (NMDs), and the topic of this thesis, is proximal spinal muscular atrophy (SMA, or 5q SMA). There is variation in disease severity, and four major types of SMA have been distinguished, classified according to age at onset and the highest achieved motor milestones (i.e. the ability to sit and walk independently), from patients with SMA type 1 being most affected and patients with SMA type 4 being least affected.

* Other terms referring to dysphagia and used in this thesis, are jaw, mastication, and swallowing problems, as well as bulbar problems (i.e. concerning the muscles of mastication, swallowing and speech) or feeding problems.

In 2015, after the Dutch SMA community had given this topic the highest priority from a range of projects, the Dutch organization for patients with neuromuscular diseases funded research into dysphagia. Dysphagia in SMA is a relatively underexposed topic but is receiving increasing attention from patient associations and social networks. Until now, research has mainly been performed using questionnaires (12, 13). The swallowing function has been studied using a video fluoroscopic swallowing study (VFSS) in six non-ambulant children with SMA type 2. VFSS showed abnormal piecemeal deglutition (in this study defined as swallowing a thin liquid bolus of 5 ml in more than 2 portions), and a post swallow residue of solid food in the hypopharynx. Their posture was characterized by a retracted head position. The amount of residue was less, when the head posture was corrected (14). The retracted head position caused by weak neck muscles, hindered the opening of the esophageal sphincter during swallowing. This resulted in post swallow residue, more for solid foods than for liquids (15). SMA is also characterized by limited maximum mouth opening, which may cause problems with biting off large pieces of food, oral hygiene, dental care, and intubation (16, 17). The underlying cause of limited maximum mouth opening is a pronounced fatty infiltration of the lateral pterygoid muscle, which is important for mouth opening (18). Another study described inefficient mastication in 15 patients with SMA, as a result of dental malocclusion, weakness of tongue and mastication muscles. Muscle fatigue, evaluated by asking the patient to hold a bite force level of 60% of the maximum for as long as possible, was also prominent compared to healthy subjects (19).

Since 2017, the introduction of genetic therapies has altered the prognosis of patients with SMA. Nevertheless, none of these therapies can cure SMA, and supportive therapy, including early detection and treatment of mastication and swallowing problems, is no less important than in the past. The aim of this thesis is to contribute to understanding dysphagia in SMA, in order to improve patient care.

In this introduction, the main characteristics of SMA, the (neuro) physiology of mastication and swallowing, the development of feeding skills, current health care, and the assessment of dysphagia will be discussed.

Etiology and classification of spinal muscular atrophy

The incidence of SMA is estimated to be 1 in 10,000 live births, and the prevalence 1-2 per 100,000 persons, although some studies have reported a higher prevalence (20). Spinal muscular atrophy (SMA) is characterized by progressive loss of alpha motor neurons in the ventral horn of the spinal cord, and brainstem nuclei (21, 22). Not all signals from the central nervous system reach the muscles, resulting in muscle weakness (Figure 1). SMA is caused by a deletion or mutation of the Survival Motor Neuron gene 1 (SMN1), on chromosome 5q. SMN1 encodes the full-length SMN protein, which is particularly important for maintaining motor neuron functions. The production of residual levels of SMN protein, in the absence of the SMN1 gene, is ensured by the presence of a second SMN gene, which is unique to humans, i.e. SMN2. SMN2 is highly homologous with SMN1, but a single C to T transition in exon 7 causes exclusion of this exon, in the large majority of SMN2 mRNA copies, and thereby the production of a shortened protein and only a small amount of full-length protein. This low level of full-length SMN protein, although sufficient to support embryonal development, is not sufficient to sustain motor neuron function after (or even shortly before) birth (23, 24). Severity of SMA varies considerably, ranging from infantile to adult onset, and correlates inversely with the number of genomic SMN2 copies (25). All patients with SMA have at least one SMN2 copy. The clinical severity scale is based on age at onset and the level of gross motor development, defined by the acquisition of two motor milestones (i.e. sitting and walking unassisted).

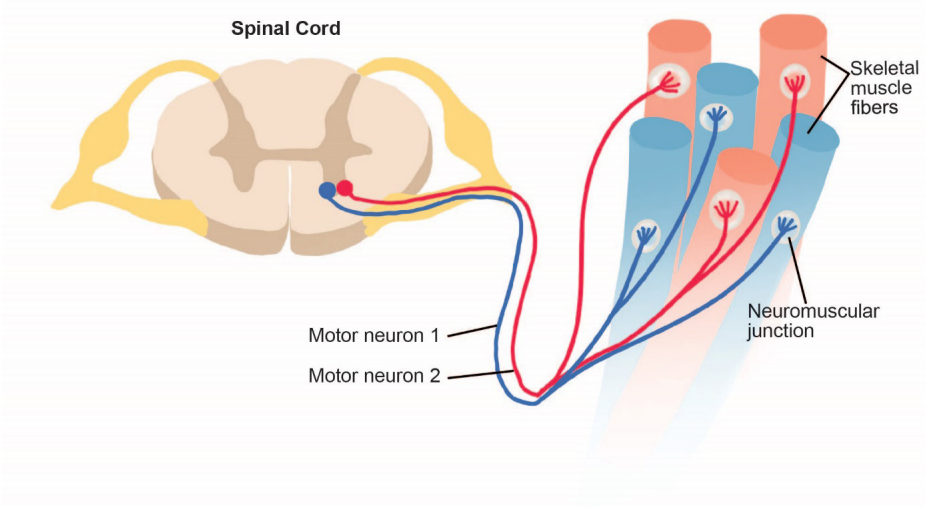

Figure 1. Schematic representation of the anterior horn of the spinal cord, motor neurons and muscle.

Four main types of SMA have been distinguished with some additional sub-classifications (Table 1) (26, 27). SMA type 1 is the most common and severe form of SMA, accounting for approximately 60% of all cases (20): most patients with SMA type 1 have 2 SMN2 copies (28). SMA type 2 constitutes the majority of prevalent cases: most patients carry 3 SMN2 copies. SMA type 3 is relatively rare and patients have 3 or 4 SMN2 copies. Adult onset SMA type 4 is extremely rare and is associated with 4 or more SMN2 copies.

Recently, genetic treatments for SMA have become available (i.e. spinraza® (nusinersen) in 2017, risdiplam and zolgensma® in 2021). Spinraza is an antisense oligonucleotide, that binds to the SMN2 pre-mRNA, alters splicing and allows the production of more full-length functional SMN protein. Risdiplam is a small molecule which also alters mRNA splicing. Zolgensma (onasemnogene abeparvovec) is a form of gene therapy that employs a viral (i.e. AAV9) vector with motor neuron tropism to reintroduce the SMN1 gene into the nucleus of human cells, in particular the alpha motor neurons of the anterior horn of the spinal cord. The best results of these novel treatments are obtained when introduced in an early, preferably pre-symptomatic stage of the disease (29-33).

Table 1. Clinical classification of spinal muscular atrophy (34).

SMA type and sub-classification	Age at onset	Highest achieved motor milestones
1	0-6 months	Never acquires ability to sit unsupported
0/1a	Prenatal/neonatal	0/1a: Symptoms in prenatal and/or neonatal period, no head control
1b (classic)	1-6 months	1b: No head control and no ability to roll over
1c	3-6 months	1c: Will usually acquire additional motor skills, such as head control or rolling from supine to prone, or at least to one side at any stage in life.
2	6-18 months	Able to sit unsupported, not able to walk
2a		2a: Unsupported sitting but not able to stand or walk even with assistance
2b		2b: in addition to unsupported sitting, able to stand or even walk a few steps, but only with assistance
3	>18 months	Able to walk unsupported
3a	18-36 months	
3b	>36 months	
4	During adulthood, i.e. > 18 years	Able to walk unsupported

Spinal muscular atrophy is characterized by damage and loss of alpha motor neurons, denervation, weakness and the appearance of skeletal muscle atrophy.

Natural history of SMA

The natural history of SMA is characterized by progressive weakness of axial and proximal limb muscles (35, 36). The respiratory muscles are also involved with predominant weakness of the intercostal muscles, but a relatively spared function of the diaphragm (27). Children with SMA type 1a and 1b demonstrate a rapid decline in motor and respiratory function, and most children have a life expectancy of less than one year (37). Children with SMA types 2 and 3, show a delay in learning to roll and sit (SMA type 2) or walk (SMA type 3). They may demonstrate slight improvement of motor function in the first year(s) of life, but after early childhood, motor function decline is the rule (35). Most patients with SMA type 3a lose their ability to walk before puberty (28). In patients with SMA types 1c to 3a, lung function gradually decreases during childhood and there is a relative stabilization in adulthood (38, 39). Virtually all patients with SMA types 1 and 2, and 40% of patients with SMA type 3a need scoliosis surgery, due to (progressive) axial muscle weakness (34).

Neurophysiology of mastication and swallowing

Swallowing (i.e. moving a bolus from the mouth to the stomach) can be described as the interaction between higher brain centers, sensory neurons and motor systems of the central and peripheral nervous systems (40). Three phases of swallowing can be distinguished: the oral phase, in which food is prepared for swallowing and transported to the pharynx; the pharyngeal phase, in which food passes the pharynx and the airway is protected against aspiration; and the oesophageal phase, in which food is transported to the stomach (41).

The neural control of swallowing involves the central cortex, subcortical regions, brain stem, cerebellum and cranial nerves (CN). CN V, VII, IX, X and XI receive sensory information from taste, temperature, and pressure sensors in the oropharynx. When food is prepared for swallowing, the rhythm and movements of mastication, depend on central pattern generators located in the medulla and pons (42, 43). Rhythmical mastication movements are induced based on sensory information from the mastication muscles. To initiate swallowing, sensory information is transferred to the nucleus tractus solitarius and the nucleus ambiguous (i.e. swallowing center), located in the medulla near the pons. In combination with input from the central cortex, this enables initiation of motor commands, sent to the CN V, VII, IX, X and XII (44). The cerebellum plays an important role in coordinating the mastication and swallowing movements (45).

Physiology of mastication

Mastication is essential to prepare a swallowable food bolus. The most prominent influencing factors of masticatory efficiency are bite force and number of functional tooth units allowing for dental occlusion (19, 46, 47). The tongue plays an important role as well, transporting the bolus between the jaws to be chewed, mixing it with saliva, and transporting it to the pharynx to be swallowed (48-50). Furthermore, the range of mandibular motion, which is facilitated by the temporomandibular joint (TMJ), is important. The TMJ is a double joint, bisected by the discus. This allows the mandible to make a combination of rotation and sliding movements in six directions: depression (enhanced by the geniohyoid, mylohyoid, digastric and the lateral pterygoid muscles) and elevation (masseter, temporalis and medial pterygoid muscles); protrusion (temporalis, lateral and medial pterygoid muscles) and retraction (posterior fibers of the masseter muscles), and side to side movements (lateral and medial pterygoid muscles) (51, 52). Previous studies have shown that weakness of (some of) these bulbar muscles is common in patients with SMA type 2 (18, 19).

Physiology of swallowing

Swallowing is a dynamic process, that requires a finely-tuned coordination of the muscles of the lips, tongue, palate, pharynx, larynx and oesophagus. After preparing and transporting the bolus to the hypopharynx, the pharyngeal phase of swallowing is initiated. The first muscle groups that initiate the swallow by contraction are the submental muscles, and posterior part of the tongue, followed by the pharynx. This contraction propels the bolus towards the upper oesophageal sphincter (UES). The velum is elevated, preventing the bolus going into the nasal cavity. The muscles of the larynx elevate the hyoid, moving it upwards and forwards, to facilitate the opening of the UES. The larynx follows this movement of the hyoid relatively simultaneously. Protection of the airway during swallowing is achieved by closing the epiglottis, and the true and false vocal folds. The food enters the oesophagus, and a peristaltic wave transports the bolus to the stomach (Figure 2) (44, 49, 53).

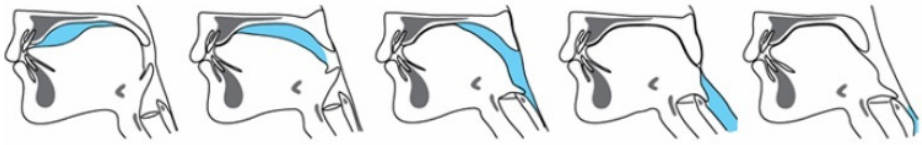

Figure 2. Normal swallowing of liquid.
Figure adapted from Matsuo and Palmer, 2008.

Development of feeding skills

SMA affects infants during a period in which they experience major developmental changes in feeding behavior. Typically developing infants are able to suck liquids after birth. From the age of 4 months they learn to ingest pureed textures and soft solid foods. At the age of six months, 80% of the daily intake consists of milk; this is only 50% by the age of 10 months. From the age of six months, lateral tongue movements develop. The infant learns to move food laterally in the mouth, enabling mastication (54). Efficiency of mastication in infants depends on several factors, such as the number of erupted teeth, bite force, the ability to control the mastication muscles, the ability to control the soft tissues (lips, cheeks, tongue) and to prepare the bolus for swallowing (55). The mastication strategies of infants aged 6 months, vary greatly. Some infants soften the bolus with saliva and initiate swallowing with sucking movements. Other infants try to munch on the bolus. From 8 months onwards, the bolus is crushed by vertical jaw movements (29). Between 24 and 30 months, horizontal jaw movements are established, mainly evoked by hard food. Maturation of mastication is characterized by a continuous decrease of mastication cycles and time needed to masticate food. By the age of 12 years, mastication reaches an adult-like pattern and strength (56, 57).

Current health care for dysphagia in SMA in the Netherlands

In multidisciplinary teams of the secondary and tertiary care centers in the Netherlands, an important role of the speech language therapist (SLT) is to determine the nature and severity of dysphagia in children and adults (58).

The international standards of care advised regular assessments of swallowing function of children with SMA by SLT before genetic therapies were available. The introduction of genetic therapies for SMA, i.e. nusinersen, risdiplam and onasemnogene abeparvovec, have further underlined the importance of SLT care, to ensure a proper bulbar function and prevention of aspiration to maximize the improved survival rate. A more recent development is the inclusion of SMA in newborn screening programs, in the Netherlands as of June 2022. Newborn screening minimizes diagnostic delays and optimizes treatment efficacy. However, it is not known whether children with the more severe forms of SMA are truly asymptomatic after birth, and to what extent bulbar muscle function remains vulnerable during life, even after early treatment. Therefore, the SLT plays an important role in care teams by monitoring infants' sucking and swallowing function, and to detect unsafe swallowing (i.e. laryngeal penetration or aspiration).

Children with SMA are monitored at least annually with quantitative mastication/swallowing tests. Adults with SMA are referred to an SLT when the patient reports mastication and/or swallowing problems.

Aims of the thesis

The main aim of this thesis is to investigate the nature and underlying mechanisms of dysphagia in SMA. We studied self-reported information about experienced mastication and swallowing problems in patients with SMA in the Netherlands. Additionally, we quantitatively assessed the mastication and swallowing function in a group of patients with SMA types 2 and 3. For infants with SMA type 1, the paucity of information about dysphagia impeded the chance of early detection of laryngeal penetration/aspiration. Therefore, we performed an observational study to describe the characteristics of dysphagia in infants with SMA type 1.

The operational aims of this thesis are:

1. To provide insights into self-reported bulbar problems across the full age and severity spectrum of SMA, and to set out the relationship with age, motor function and active maximum mouth opening.
2. To describe characteristics, symptoms and underlying mechanisms of mastication and swallowing problems, in adolescents and adults with SMA types 2 and 3.
3. To describe characteristics and symptoms of swallowing problems in infants with SMA type 1, and explore the relation with motor function.

All in order to develop best practice recommendations.

Assessment of dysphagia

In this thesis, we used a combination of self-reported, clinical and instrumental assessments to investigate mastication and swallowing problems in SMA. The questionnaire DDD(p)NMD was developed by a group of SLTs involved in the care of patients with NMD, with the aim of detecting problems with mastication and swallowing (59) (Appendix). For clinical examination, we used validated tests to assess maximum swallowing volume, swallowing speed, masticatory efficiency, masticatory fatigability (60-63). To assess the underlying reasons for mastication/swallowing problems, we used instrumental assessments. Efficiency and safety of swallowing was assessed by VFSS, using scales to score pharyngeal residue and laryngeal penetration/aspiration (64, 65). The structure of the bulbar muscles was assessed by qualitative muscle ultrasound (66).

We combined the test results with the patient's medical data of the patient regarding active maximum mouth opening, and functional motor scales, such as the Hammersmith functional motor scale (HFMS) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) (67-69).

Outline of this thesis

The fact that specific problems of bulbar function have not been elucidated in patients with SMA, has led to the studies presented in this thesis.

Following the general introduction (chapter 1), we report the assessment of the self-reported bulbar problems, in 118 patients with SMA types 1-4 (chapter 2). Chapter 3 describes efficiency and endurance of mastication in patients with SMA types 2 and 3. Chapter 4 describes efficiency and safety of swallowing in patients with SMA types 2 and 3. Chapter 5 looks at dysphagia in 16 infants with SMA type 1. Chapter 6 is a general discussion of the results of this thesis.

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Chapter 2

Bulbar problems self-reported by children and adults with spinal muscular atrophy

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Abstract

Background

Spinal muscular atrophy (SMA) is a hereditary motor neuron disorder, characterised by the degeneration of motor neurons and progressive muscle weakness. It is caused by the homozygous loss of function of the survival motor neuron (SMN) 1 gene. SMA shows a wide variability of disease severity.

Objective

To investigate self-reported bulbar problems in patients with SMA, and their relationship to age, functional motor scores and active maximum mouth opening.

Methods

We used the Diagnostic List of Dysphagia and Dysarthria in (pediatric) patients and relevant recent clinical data from the national SMA database.

Results

The 118 included patients with SMA frequently reported jaw problems (34%), fatigue associated with mastication (44%), choking (56%) and intelligibility problems (27%). Jaw, mastication and swallowing problems frequently occurred in combination with each other. There was an increase of reported bulbar problems in patients with SMA type 3a, older than 30 years of age, compared to younger patients of this SMA type.

The Hammersmith Functional Motor Scale Expanded scores showed a negligible correlation with jaw and mastication problems, a low negative correlation with swallowing problems and a moderate negative correlation with intelligibility problems. Reduced mouth opening showed a significant, but low correlation with bulbar complaints in patients with SMA type 2.

Conclusions

Fatigue associated with mastication and swallowing problems were frequently reported complaints. Patients 30 years and older with milder forms of SMA showed an increase of self-reported bulbar problems. The results of this study show that it is important to be alert on bulbar problems in patients with SMA.

Introduction

Proximal spinal muscular atrophy (SMA) is a hereditary motor neuron disorder caused by the homozygous loss of function of the survival motor neuron1 (SMN1) gene. It is characterized by large variability in disease severity as reflected by the SMA classification system, that distinguishes four SMA types (i.e. type 1 – 4) based on age at onset and the acquisition of specific motor milestones (i.e. sitting and walking independently) (1-3). SMA is characterized by degeneration of alpha-motor neurons in the spinal cord and dysfunction of the neuromuscular junction (4). This causes progressive muscle weakness that is most pronounced in proximal muscle groups of the extremities, axial and respiratory muscles (1, 5). Post-mortem studies also showed abnormalities of brainstem motor nuclei, suggesting that bulbar functions (of speech and swallowing) are affected in a caudal to rostral gradient (6).

The number of studies on bulbar functions such as mastication, swallowing and speech, in SMA is relatively small (7-12). Instrumental swallowing studies have shown abnormalities, i.e. piecemeal deglutition, post-swallow residue in the valleculae and above the upper esophageal sphincter, but have only been performed in small numbers of patients with relatively severe motor deficits (11, 12). Questionnaire-based studies have explored the prevalence of bulbar problems (10, 13, 14). These studies showed that a substantial group of patients reported problems with biting, mastication, mouth opening and swallowing, but they did not cover the full spectrum of SMA. Finally, magnetic resonance imaging (MRI) studies have shown fatty infiltration of specific bulbar muscle groups (10).

The aims of this study were to explore some important questions that remain to be answered. These include: 1) what is the prevalence of self-reported problems of mastication and swallowing across the full spectrum of SMA?; 2) what is the prevalence of speech problems?; 3) are age, the level of motor function and active maximum mouth opening (aMMO) correlates of bulbar dysfunction? In addition, we explored the test-retest reliability of the Diagnostic List of Dysphagia and Dysarthria in (pediatric) patients with Neuromuscular Diseases (DDD(p)NMD).

Patients and methods

Patients

We invited 185 patients with a genetically confirmed diagnosis of SMA registered in the Dutch SMA registry, to complete a questionnaire about feeding and swallowing problems. In case of young children, caregivers were asked to fill in the questionnaire. Patients who gave informed consent filled in an online questionnaire using a unique personal access code, which they had received by email. Patient characteristics are summarized in Table 1.

The Dutch SMA registry contains detailed data collected as part of an ongoing population-based prospective study. We classified SMA types according to the following criteria: type 1: onset before 6 months, does not learn to sit; type 2: onset between 6-18 months, able (or has been able) to sit independently; type 3a: onset between 18-36 months, able (or has been able) to walk without support; type 3b: onset after > 3 years, able (or has been able) to walk without support; type 4: onset > 30 years) (3). We also used the most recent entries in the registry regarding the need for (non-) invasive ventilation, aMMO and the HFMS(E) scores, a widely used score that reflects (remaining) motor function in SMA (20). For aMMO, which reflects fatty infiltration of specific bulbar muscle groups, patients were asked to open their mouth as wide as possible. The distance was measured between the right maxillary and mandibular incisors as described previously (8,9).

We defined swallowing problems as problems with moving food or drinks from the oral cavity to the oesophagus. Choking was defined as a blockage of the airway by foods or drinks.

The Medical research and Ethics Committee (METC) of the University Medical Center Utrecht was consulted and approved the study protocol according to the Dutch legislation on clinical studies.

The questionnaire

The Diagnostic List of Dysphagia and Dysarthria in (pediatric) patients with Neuromuscular Diseases (DDD(p)NMD) was originally developed by a group of speech-language therapists involved in the care of dysphagia and dysarthria in neuromuscular diseases with the aim of identifying feeding and swallowing problems (appendix 1) (15). The questionnaire consists of 39 dichotomous questions and 2 multiple choice questions, including specific questions about jaw function, mastication and swallowing problems, the need to adapt food consistency, mealtime duration, requirement for tube feeding, weight issues, occurrence of respiratory infections, and intelligibility problems in particular

complaints about insufficient loudness of the voice, shortness of breath when talking, getting tired when talking.

To compose a severity score of the reported bulbar problems, four composite scores were created by adding up the reported jaw (4 items), mastication 3 items), swallowing (5 items) and intelligibility problems (6 items). A total composite score of the items related to feeding was created by adding up the composite jaw, mastication and swallowing scores (12 items).

To assess the reproducibility of the questionnaire, a random sample of 30 patients was asked to fill in the questionnaire a second and a third time with a time interval of four weeks.

Statistical Analysis

Descriptive statistics were used for patient characteristics and questionnaire responses (n, %). For analysis we combined the subgroups SMA type 3b and 4, as subgroup 4 was very small (n=3), and disease course is largely comparable.

Associations between bulbar problems were tested using Fisher Exact Test for categorical data. Bulbar problems among different age-groups were presented as frequencies. The correlation between the reported jaw, mastication and swallowing problems and data about functional motor abilities were analysed using Spearman's rank test, as HFMS(E) is an ordinal scale. The correlation between aMMO and reported jaw, mastication and swallowing problems was analysed using Kendall's Tau because of the size of the patient subgroups (n=27 and n=14).

To evaluate test-retest reliability, the agreement of the dichotomous items was analyzed with a two-way random effects intraclass correlation coefficient (ICC) and a Cohen's kappa. The level of significance for two-tailed p-values was set at <0.05. All analyses were performed in SPSS 22 (IBM,SPSS statistics version 22, Chicago, IL, USA).

Results

Patients

In total, 118 patients (or their caregivers) (age range 1-75 years) completed and returned the questionnaire (response rate: 64%). We assumed that adult patients reported their own experiences and that parents did this on behalf of or together with their children. No significant differences in gender (p= 1.00), age (p= .21), SMA type (p= .58), use of (non-) invasive ventilation (p= .51) or HFMS(E) scores (p= .36) were detected between the responders and non-responders.

The study was conducted from September 2016 to November 2017, a period in which nusinersen was not reimbursed in the Netherlands. Patient characteristics are summarized in Table 1.

Table 1. Patient Characteristics.

	SMA 1[a] (N=11)	SMA 2 (N=55)	SMA 3a (N=26)	SMA 3b/4 (N=26)
Gender (M:F)	6 : 5	22 : 33	10 : 16	16 : 10
Ambulant, n (%)	NA	NA	10 (38)	17 (65)
Age < 20 years : Age 20-75 years	9 : 2	30 : 25	9 : 17	2 : 24
Age (in years), mean (range)	11.8 (1-38)	20.7 (1-73)	33.3 (6-64)	46.3 (16-75)
< 5 years n (%)	5 (45)	11 (20)		
5-9 years n (%)	2 (18)	5 (9)	5 (19)	
10-19 years n (%)	2 (18)	14 (25)	4 (15)	2 (8)
20-39 years n (%)	2 (18)	18 (33)	6 (23)	6 (23)
40-59 years n (%)		5 (9)	9 (35)	15 (57)
≥ 60 years n (%)		2 (4)	2 (8)	3 (12)
(Partial) tube feeding, n (%)	6 (55)	8 (15)	1 (4)	0
Non-invasive Ventilation, n (%)	3 (27)	13 (24)	(4)	0
Invasive ventilation	4 (36)	1 (2)	(8)	0
HFMS(E), mean (range)	0 (0-1)	8 (0-40)	20 (0-57)	35 (2-66)

Abbreviations: SMA, spinal muscular atrophy; M, male; F, female; n, number of patients; HFMS(E), Hammersmith Functional Motor Scale Expanded.
[a]All SMA type 1 patients in this study survived infancy.

Reported bulbar problems

Mastication, swallowing and intelligibility problems were reported more frequently by patients with the more severe forms of SMA, but jaw problems were reported to an equal degree across the different types of SMA. Detailed answers on the questionnaire are depicted in Table 2. The most common

bulbar problems reported by all patients, irrespective of SMA type, were 'biting off a large piece of food' (34%); 'fatigue associated with mastication' (44%); 'choking' (56%) and 'a weak voice' (27%). Swallowing problems (i.e. swallowing food and the feeling of food getting stuck in the throat) were mainly related to solid food. There was a significant association between jaw and mastication problems ($p < .001$), jaw and swallowing problems ($p < .001$), and mastication and swallowing problems ($p < .001$).

The questionnaire revealed various issues related to feeding and swallowing problems, like the need to adapt food (cutting into small pieces, pureeing food or avoiding hard foods), meal duration, getting tired when eating, eating or drinking insufficiently and dreading mealtimes (Figure 1). Nearly half of the 55 patients who adapted their food did not manage to finish their meals within 30 minutes. In addition, a considerable number of patients reported difficulty eating enough (8%), drinking enough (14%) or eating and drinking enough (3%), but did not receive (partial) tube feeding.

Table 2a. Prevalence of jaw and mastication problems.

	SMA 1[a] (N=11)	**SMA 2 (N=55)**	**SMA 3a (N=26)**	**SMA 3b/4 (N=26)**	**All (N=118)**
Jaw Problems					
Biting off a large piece of food, n (%)	3 (27)	21 (39)	9 (35)	7 (27)	40 (34)
Yawning, n (%)	1 (9)	4 (7)	3 (12)	6 (23)	14 (12)
Laughing, n (%)	1 (9)	1 (2)	2 (8)	4 (15)	8 (7)
Jaw problems when tired, n (%)	1 (9)	8 (15)	3 (12)	3 (12)	15 (13)
Jaw problems after waking up, n (%)	0	1 (2)	0	2 (8)	3 (3)
Sum of 5 jaw problems, median (range)	0 (0-3)	0 (0-4)	0 (0-4)	0 (0-5)	
Mastication Problems					
Difficulty with mastication, n (%)	7 (64)	23 (42)	5 (19)	4 (15)	39 (33)
Fatigue associated with mastication, n (%)	8 (73)	28 (51)	8 (31)	8 (31)	52 (44)
Jaw problems, eating hard foods, n (%)	3 (27)	15 (28)	4 (15)	6 (23)	28 (24)
Sum of 3 mastication problems, median (range)	2 (0-3)	1 (0-3)	0 (0-3)	0 (0-3)	

Table 2b. Prevalence of swallowing and intelligibility problems.

	SMA 1[a] (N=11)	SMA 2 (N=55)	SMA 3a (N=26)	SMA 3b/4 (N=26)	All (N=118)
Swallowing Problems					
Difficulty swallowing food, n (%)	7 (64)	23 (42)	8 (31)	3 (12)	41 (35)
Choking more than once a day, n (%)	9 (82)	30 (55)	15 (58)	12 (46)	66 (56)
Coughing with solid foods, n (%)	7 (64)	13 (24)	8 (31)	7 (27)	35 (30)
Coughing with liquids, n (%)	2 (18)	4 (7)	1 (4)	1 (4)	8 (7)
Feeling food stuck in throat, n (%)	5 (46)	27 (49)	9 (35)	8 (31)	49 (42)
Sum of 5 swallow problems, median (range)	3 (0-5)	2 (0-5)	1.50 (0-5)	0.5 (0-4)	
Intelligibility Problems					
Short of breath when talking, n (%)	5 (46)	13 (24)	4 (15)	5 (19)	27 (23)
Fatigue associated with talking, n (%)	4 (36)	9 (16)	4 (15)	2 (8)	19 (16)
People ask to repeat,n (%)	5 (46)	14 (26)	5 (19)	4 (15)	28 (24)
People ask to repeat in noisy environment, n (%)	8 (73)	23 (43)	11 (42)	5 (19)	47 (40)
Sore throat due to talking, n (%)	2 (18)	11 (20)	6 (26)	6 (23)	25 (21)
Suffering from a weak voice, n (%)	3 (27)	19 (35)	6 (23)	3 (12)	31 (27)
Sum of 6 intelligibility problems, median (range)	2 (0-6)	1 (0-6)	0.5 (0-6)	0 (0-6)	

Data are given as n (%) or median (range).

[a]All SMA type 1 patients in this study survived infancy.

Influence of age on reported bulbar problems.

We investigated bulbar problems among different age groups stratified for SMA type (Figure 2). Patients of all age-groups with SMA type 2 reported jaw, mastication, swallowing and intelligibility problems. Almost all patients with SMA type 3a aged 30 years and older (n=16) reported swallowing problems. Other bulbar problems were also frequently reported in this age group of SMA type 3a patients, in particular jaw (60%), mastication (33%) and intelligibility problems (60%).

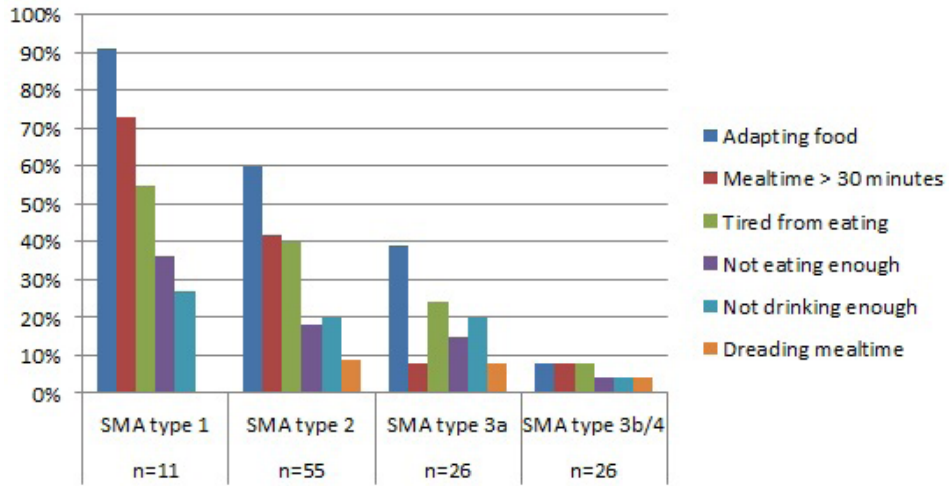

Figure 1. Feeding related issues reported by patients with SMA type 1, 2, 3a, 3b/4 (N=118).

Patients with SMA type 3b/4 aged 30 years and older (n=21) reported jaw (38%), mastication (33%), swallowing (57%) and intelligibility problems (38%).

Functional motor abilities and reported bulbar problems

The HFMS(E) score (n=101) showed a negligible correlation with reported jaw problems (r_s=-.28, p=.005) and mastication problems (r_s=-.27, p=.006); a low negative correlation with swallowing problems (r_s=-.48, p=< .001) and a moderate negative correlation with intelligibility problems (r_s=-.54, p=< .001).

Active maximum mouth opening in relation to reported jaw, mastication and swallowing problems

The correlation between aMMO and reported bulbar problems (total composite score, see methods) in patients with SMA type 2 (n=27) was low (τ=-.39, p= .007). There was no significant correlation between aMMO and reported bulbar problems in patients with SMA type 3a (n=14) (τ=.083, p=.694) and 3b/IV (n=17) (τ=-.016, p=.933) (Figure 3).

Test-retest reliability of the questionnaire

Fourteen out of 30 patients (or their caregivers) (47%) returned the questionnaire a second and third time. The Intra rater reliability of the Diagnostic List of Dysphagia and Dysarthria in (pediatric) patients with Neuromuscular Diseases (DDD(p)NMD) was high for the total score (n=14, ICC = .94, (CI .80 – .98), and sub scores of jaw problems (ICC = .96, (CI .87 - .99),

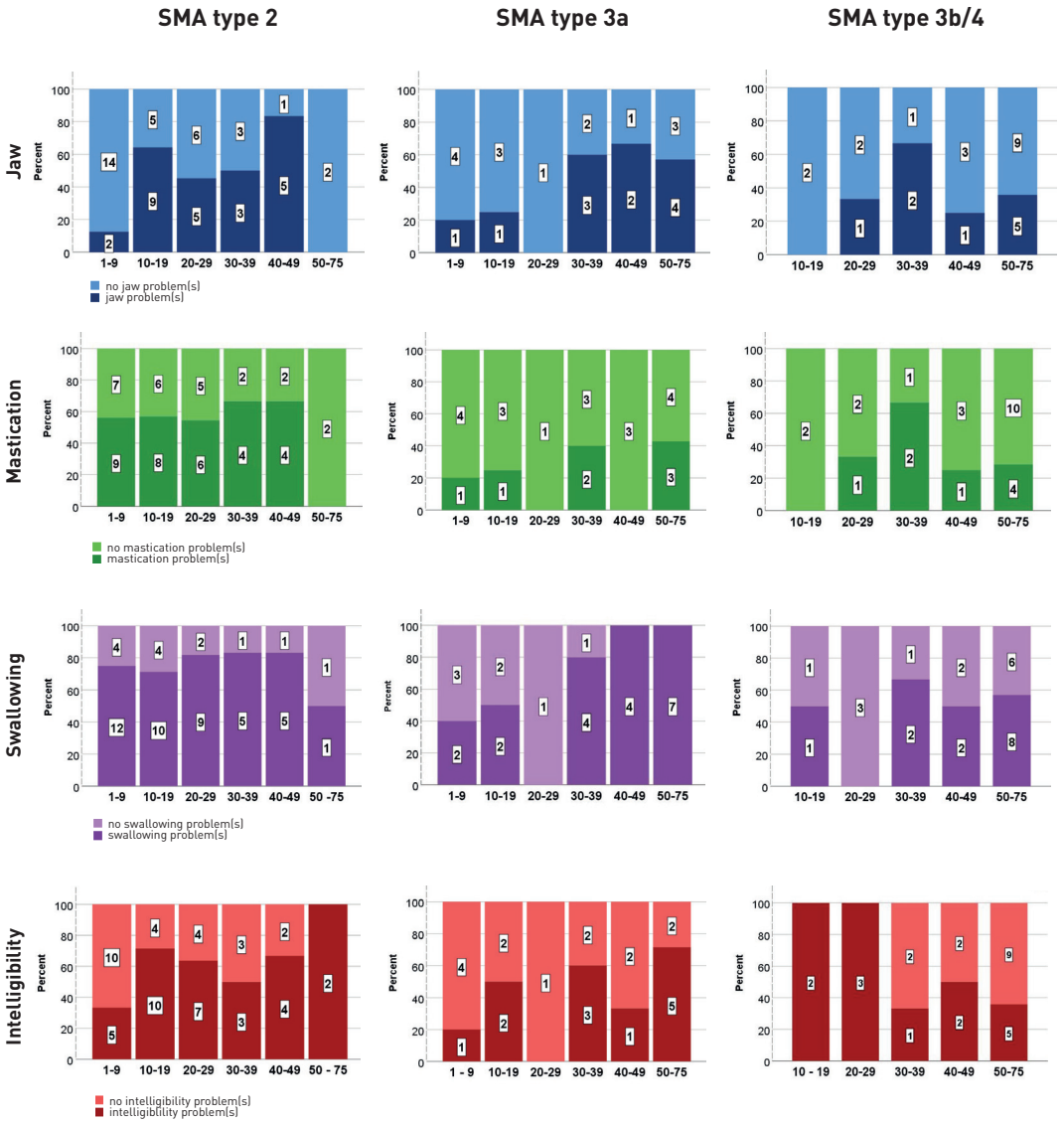

Figure 2. Reported bulbar problems in SMA type 2 , 3a, 3b/4, across different age-groups per type SMA.

mastication problems (ICC = .99, CI .97 – 1.00), swallowing problems (ICC = .95, (CI .84 - .98) and speech problems (.ICC = .91, (CI .73 - .97). The Cohen's Kappa was > .80 for 14 out of 27 items and .60 - .79 for six items (i.e. problems swallowing food, mealtime longer than 30 minutes, choking, tired when eating, jaw problems when laughing and sore throat when speaking). The Cohen's kappa was < .60 for three items (i.e. coughing with solid foods, jaw problems when biting off large food, sufficient voice volume). The Cohen's Kappa could not be calculated for four items (coughing when drinking, excessive belching, eating enough, (partial) tube feeding), as a result of a correction for chance agreement when too many answers fall into the same category (for example the majority of the patients answered 'coughing when drinking' with 'no').

Discussion

This study aimed at documenting self-reported bulbar problems in SMA. It adds important new information to previous studies. First, we included patients across the entire age and severity spectrum of SMA. Second, the questionnaire used (DDD(p)NMD), which overlaps with those used previously (13, 14), showed good test-retest characteristics. Finally, we studied correlations with HFMS(E) and aMMO, scores that reflect the overall level of motor function and of bulbar muscles, respectively.

A significant proportion of SMA patients, including aging patients with milder variants, experience bulbar problems. This is important to note, as previous studies have primarily identified bulbar problems in younger and more severely affected patients (13, 14).

Jaw, mastication and swallowing problems frequently occurred in combination with each other. This implies that when patients report jaw, mastication or swallowing problems, this may reflect a wider range or combination of bulbar problems. We show that fatigue associated with mastication is relatively common as suggested previously (5, 7). We also found reduced intelligibility interfering with communication in daily life, an item that was not studied previously, in a large proportion of patients. Fatigue associated with mastication and swallowing problems may preclude some patients from achieving sufficient intake.

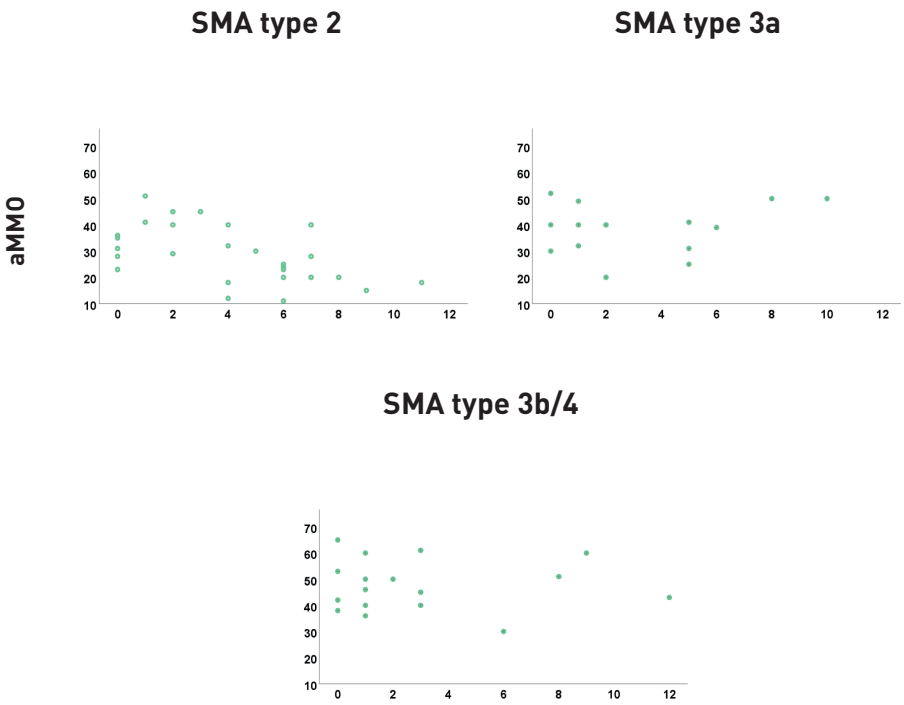

Figure 3. Relationship between aMMO in millimeters (n=93) and the total composite score (0-12 points) in patients with SMA type 2, 3a and 3b/4. aMMO = active maximum mouth opening. Sum score of jaw, mastication, and swallowing problems (x axis).

In addition to exploring the prevalence of specific bulbar problems, we studied correlates of bulbar dysfunction. Age correlated with the presence of bulbar complaints. This suggests that swallowing and mastication problems, which are relatively uncommon among younger patients with SMA type 3a and 3b/4, may become more common after the age of 30 years, although we cannot exclude the possibility that this difference is caused by caregiver reporting in younger, and self-reporting in older patients. We also found a low to moderate negative correlation of swallowing and intelligibility problems with HFMS(E). Motor scores decline with longer disease duration, which may help to explain progressive bulbar complaints with advancing age (16-19).

Finally, we hypothesized that aMMO is more closely associated with bulbar dysfunction. The correlation between aMMO and bulbar problems

was - similar to previous observations (10) - significant for patients with SMA type 2, but not in type 3a and 3b/4. This suggests that the value aMMO in the assessment of bulbar problems is limited to type 2.

Questionnaires, estimates of motor scores and aMMO may be tools to identify patients with bulbar function limitations. However, the true prevalence of bulbar function problems is probably even higher than self-reported, as patients may adapt to gradually worsening function. For example, problems with mouth opening were dramatically underreported (8-10). Additional validated instruments to detect bulbar dysfunction are needed, or at least a like-for-like comparison of instrumental swallowing studies and questionnaire results.

One of the strengths of our study is the relatively large sample size that covers the full spectrum of SMA. This allowed us to document bulbar problems in patients with all ages, milder forms of SMA and long disease duration. Our data also identified intelligibility problems and fatigability of bulbar muscles that may have been overlooked previously. Finally, we showed that the degree of reproducibility of the questionnaire is probably good.

This study also has limitations. Although the response rate is satisfactory, and no significant differences were detected between responders and non-responders, it is possible that patients with relatively severe bulbar complaints have responded. We therefore cannot exclude that this may have led to an overestimation of bulbar problems. Another limitation is that patients were not asked about their motor possibilities to bring food to the mouth, or to perform oral care independently. However, the questionnaire consists of questions that clearly refer to mastication and swallowing. The question about the ability to brush teeth had the intention to reveal limitations in jaw opening. Since patients may have interpreted this question as the ability to brush their teeth independently, it was excluded from analysis. Statistical power of subgroup analyses was limited as in previous studies. Finally, the use of self-reporting questionnaires has its limitations, not in the least as patients and caregivers may report differently. Nonetheless, our work shows that awareness of bulbar problems in all SMA types and ages needs improvement.

Future studies to further delineate bulbar problems in SMA may benefit from combining more objective measures for bulbar dysfunction, e.g. video-fluoroscopic swallowing studies or imaging of bulbar muscles, with subjective questionnaires.

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Chapter 3

Mastication in patients with spinal muscular atrophy types 2 and 3 is characterized by abnormal efficiency, reduced endurance and fatigue

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Abstract

Objective

This study aims to understand the nature and underlying mechanisms of mastication problems in patients with SMA types 2 and 3 with reported bulbar problems.

Methods

This cross-sectional study characterizes mastication problems using clinical and instrumental assessments in patients with spinal muscular atrophy (SMA) types 2 and 3 with self-reported bulbar problems. We included 27 patients (aged 13 – 67 years), 18 with SMA type 2 and 9 patients with SMA type 3 (of whom three were still ambulant) and applied a questionnaire, clinical mastication tests (TOMASS and 6-min mastication test), and muscle ultrasound of the mastication muscles.

Results

Non-ambulant patients demonstrated inefficient mastication as reflected by median z-scores for masticatory cycles ($z = 1.8$), number of swallows ($z = 4.3$) and time needed to finish the cracker ($z = 3.4$), and limited endurance of continuous mastication as demonstrated by the median z-scores of the 6-min mastication test ($z = -1.5$). Patients reported increased fatigue directly after the 6-min mastication test as well as 5 min after completing the test ($p < 0.001$; $p = 0.005$). Reduced maximum mouth opening was associated with mastication problems ($p < 0.001$). Muscle ultrasound of the mastication muscles showed an abnormal muscle structure in 90% of both ambulant and non-ambulant patients.

Introduction

Hereditary proximal spinal muscular atrophy (SMA) is caused by a loss of function of the survival motor neuron SMN1 gene and is characterized by loss of alpha-motor neurons in the brainstem and spinal cord. Muscle weakness is most pronounced in axial, respiratory and proximal muscle groups of the limbs (1). Severity shows a wide range, from infantile (SMA type 1) and childhood onset (types 2 and 3) to adult onset (type 4). Natural history studies of SMA have shown a progressive decline in motor function and muscle strength over the course of months (type 1) or years (type 2-4) (2,3).

Effects of brainstem involvement on facial and bulbar functions have been described (4,5,6). Fasciculations of the tongue and contractures of the mandibular joint that cause reduced maximum mouth opening are well known clinical characteristics of SMA, but more complex functions such as mastication have not been analyzed in detail despite their importance and relevance for daily life (7-10). Questionnaire studies have shown that patients frequently report mastication problems, but their prevalence and severity have not been investigated clinically. Mastication problems may increase the risk of inefficient food passage and blockage of the airway and may negatively impact the social function of eating. This may result in avoidance of food and meals and lead to malnutrition (11,12,13). In this study, therefore, we aimed to gain further insight into the efficiency and endurance of mastication (14,15) in patients with SMA types 2 and 3 by means of questionnaires and clinical tests. We used muscle ultrasound to investigate underlying abnormalities of bulbar muscle groups (16).

Methods

Participants

We performed a cross-sectional study between August 2018 and August 2019, applying diagnostic criteria of the SMA Consortium for the classification SMA types 2 and 3 (17-19), i.e. onset between the ages of 6 and 18 months and the ability to sit independently at some stage of life for SMA type 2 and onset after the age of 18 months and the ability to walk without support at some stage of life for SMA type 3.

Patients (12 years and older) listed in the Dutch SMA registry who participate in an ongoing population-based study on SMA were approached by letter. Those patients with SMA type 2 or 3 who mentioned bulbar

problems (i.e. fatigue or difficulty with chewing; coughing when swallowing liquid or solid foods; food getting stuck in the throat; the need for adaption of food; mealtimes longer than 30 min; tube feeding required) were invited to participate.

None of the patients included in the study were treated with nusinersen, risdiplam or AAV-gene therapy. Six patients used pyridostigmine, but not on the day of the study assessments (20,21).

The Medical research and Ethics Committee (METC) of the University Medical Center Utrecht approved the study protocol according to the Dutch legislation on clinical studies (METC 17-718). Informed consent was obtained from the patients or from the parents and patients, if they were younger than 16 years.

Study design

Mastication was assessed, using a combination of a self-report questionnaire, clinical observation, clinical and instrumental tests (e.g. video fluoroscopic swallowing study and muscle ultrasound). Two experienced speech and language therapists (AMBH and LEH) performed the assessments. One of them carried out the test while the other video-taped the patient. Outcome scores were based on consensus.

Questionnaires and clinical scales

Bulbar problems were assessed with the Diagnostic List of Dysphagia and Dysarthria in (pediatric) patients with Neuromuscular Diseases (DDD(p) NMD). This questionnaire, which has been used previously for patients with SMA (13), consists of 39 yes/no-questions and two multiple choice questions about masticatory-, swallowing and jaw issues and consequences for mealtime duration, food adaptations, weight, and the occurrence and frequency of respiratory infections.

We used the functional oral intake scale (FOIS), an ordinal scale that reflects functional oral intake of patients with dysphagia. The scores range from 1 (nothing by mouth) to 7 (total oral diet with no restrictions) (22).

Clinical mastication tests

Efficiency of mastication was assessed using the test of mastication and swallowing solids (TOMASS) (14). Patients had to eat a single portion of a standardized cracker (4.5 x 4.5 cm) as quickly as possible, but at a safe pace, and to say 'yes' when they were finished. We video-taped the patient laterally to determine the number of discrete bites, masticatory cycles (i.e. one cycle

is the opening and closing of the jaws), and swallows per cracker, as well as the total time needed to finish the cracker (timed from the moment the cracker passed the bottom lip until the patient indicated that he was finished). Results were compared with normative Dutch data using z-scores (14, 23).

Endurance of continuous mastication was assessed with the Six-Minute Mastication test (6MMT) (15). We used this test to capture endurance, which is often reduced in patients with SMA, as shown by a decline in physical performance over a given time of repetitive task performance (24). For the test, the patient masticates continuously on a chewing tube (Theratube©, also known as Thera-tubing©, level 4 for adults) for a period of six minutes. This test was the last of the battery of assessments to avoid any influence on the performance of other tests. We video-taped patients laterally to enable proper visualization of the masticatory movements. We documented the total number of masticatory cycles and the % difference in masticatory cycles between minute 1 and minute 6 as outcome measures for endurance. In addition, we rated rhythm of mastication (rhythmic, variable, not rhythmic), and magnitude of movements (normal, large or small masticatory movements). To measure the subjective perception of fatigue and pain of masticatory muscles we used a visual analogue scale (VAS, 0 = no pain, 10 is severe pain; 0 = no fatigue, 10 = severe fatigue) directly after the test and 5 min later. Patients were allowed to see their first score when giving their second score. VAS-scores were compared with the Dutch normative data of the 6MMT (15).

Active maximum mouth opening and dental occlusion

Active (unassisted) maximum mouth opening (aMMO) was assessed with a TheraBite® range of motion scale (Atos Medical AB, Hörby, Sweden). We measured the distance between the mesioincisal angle of the right upper and lower front teeth plus the overbite while the patient opened the mouth as wide as possible. A maximum mouth opening of 40 mm was considered as the lower limit of normal (8, 25). We documented dental occlusion using a mouth spreader. Occlusal contacts were classified as normal, anterior/posterior open bite or cross bite.

Muscle ultrasound

Muscle ultrasound was performed to visualize the structure of the masticatory muscles (m. masseter and m. temporalis) and tongue muscles using an Affiniti 70 Philips ultrasound system (Philips, the Netherlands) with a 12-5 MHz transducer. For the masseter muscle, the probe was placed on the cheek perpendicular to the jaw line (mandible) with a depth setting of 4 cm. For the

temporalis muscle the probe was placed on the upper border and parallel to the zygomatic arch and moved cranially until the muscle was visible. For the tongue we used a broadband linear intra operative (so called hockey stick) 14-5 MHz transducer (16). We stored data as DICOM images. The images were scored qualitatively based on consensus (author LEH with another speech and language therapist experienced in muscle ultrasound images) either as 'normal structure and echogenicity', 'moth-eaten pattern with increased echogenicity' or 'increased echogenicity without moth-eaten pattern' (Figure 1) (26,27). The raters were blind for patient information and did not have access to results of other assessments of the study.

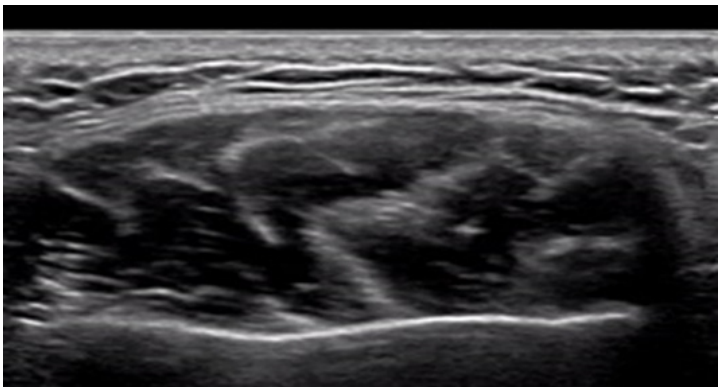
Statistical analysis

Categorical variables were specified as number and percentage or median and range. The results of the self-reported mastication problems (questionnaire) and mastication tests were stratified according to the level of motor function: non-ambulant versus ambulant patients.

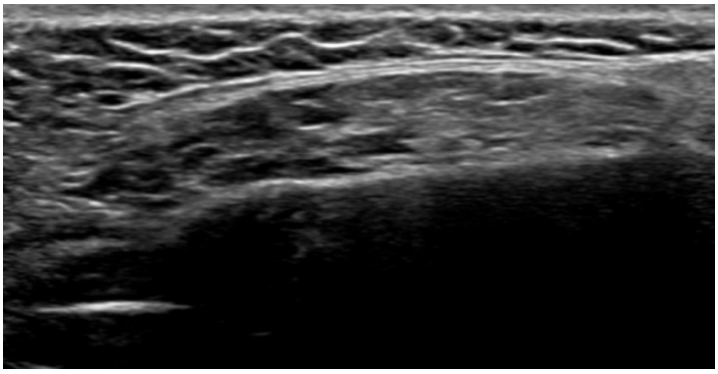
Results of the TOMASS were presented as z-scores. The number of bites, mastication cycles, swallows and total time (in seconds) to eat the cracker were standardized into z-scores using Dutch normative data, collected from 134 healthy children (4-18 years of age) and 124 healthy adults (20 – 80 years of age) (28). Z-scores of the 6 MMT for total number of mastication cycles, difference in masticatory cycles between minute 1 and minute 6, and VAS scores for pain and fatigue were obtained based on Dutch normative data, collected from 215 healthy subjects (9-80 years of age) (15). Median VAS scores for pain and fatigue of the SMA patients and healthy subjects were compared using a one-sample Wilcoxon Signed-rank Test.

Associations between the questionnaire ('do you adapt food'; 'difficulty with chewing') and efficiency of mastication (dichotomized z-scores (</> 1.5) of the TOMASS' 'total time needed to finish the cracker') were tested using Fisher Exact Test for categorical data.

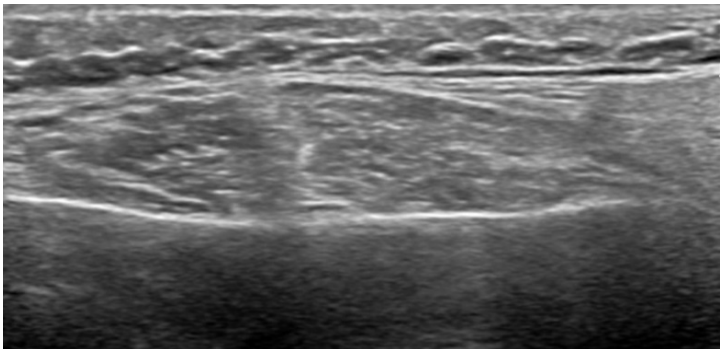
The relation between aMMO and masticatory skills was explored using univariate linear regression. Due the right-skew in TOMASS time, we regressed the aMMO with the natural logarithm of time. Results were translated to the original scale to improve interpretation. A p-value of < 0.05 was considered as significant. Data were analyzed using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).



Score 1. Normal structure and echogenicity



Score 2. Moth-eaten pattern with increased echogenicity



Score 3. Increased echogenicity

Figure 1. Muscle ultrasound images of the masseter muscle, with normal structure and echogenicity (score 1), increased echogenicity with an inhomogeneous, moth-eaten pattern (score 2), and increased echogenicity, where muscle outline fade and disappear (score 3).

Results

Patient characteristics are described in Table 1. We included 18 patients with SMA type 2, and 9 patients with SMA type 3 (3 ambulant, 6 non-ambulant).

Table 1. Patient characteristics.

	SMA type 2 (n=18)	SMA type 3 (n=9)
Sex (M: F)	5:13	3:6
Age in years, median (range)	32 (13 – 61)	54 (30– 67)
Non-ambulant: Ambulant	18:0	6:3
Current respiratory status: No respiratory management, n (%) Non-invasive ventilation, n (%) Invasive ventilation, n (%)	14 (78) 4 (22)	6 (67) 2 (22) 1 (11)
aMMO (in mm) non-ambulant patients, median (range)	24 (16 – 53)	37 (21 – 43)
aMMO (in mm) ambulant patients, median (range)	n/a	51 (50 – 55)
Anterior open bite	4 (22)	2 (22)*
Posterior open bite	5 (28)	1 (11)
Cross bite	13 (72)	4 (44)
FOIS, median (range)	5 (27)	5 (57)

*Dental occlusion of 1 patient missing
Abbreviations: F= female; M= male; aMMO = active maximum mouth opening; mm = millimeter; n/a = not applicable; FOIS =functional oral intake scale

Questionnaire

Twenty-four non-ambulant patients (18 patients with SMA type 2 and 6 patients with SMA type 3) reported difficulty with one or more of the items 'biting off hard food' (71%), 'difficulty with chewing' (67%), and 'fatigue while chewing' (71%). A majority adapted food by pureeing or cutting solid food into small pieces (88%) or reported mealtimes lasting longer than 30 min (54%). Eight patients (33%) reported myalgia, cramp or tiredness in the jaws when eating or when tired.

The three ambulant patients did not mention difficulty with mastication, difficulty biting off hard food, adapting food, or longer mealtimes. One ambulant patient reported fatigue when chewing.

Test of Mastication and Swallowing Solids (TOMASS)

The results of the TOMASS are summarized in Table 2. Z-scores of < 1.5 (TOMASS) were considered normal. The number of discrete bites of the non-ambulant patients was similar to that of healthy subjects (median z-score 0.4), but on average the non-ambulant patients needed more masticatory cycles (median z-score 1.8), swallows (median z-score 4.3) and time to finish the cracker (median z-score 3.4). Efficiency of mastication in non-ambulant patients with SMA type 3 was comparable to patients with SMA type 2 (Figure 2).

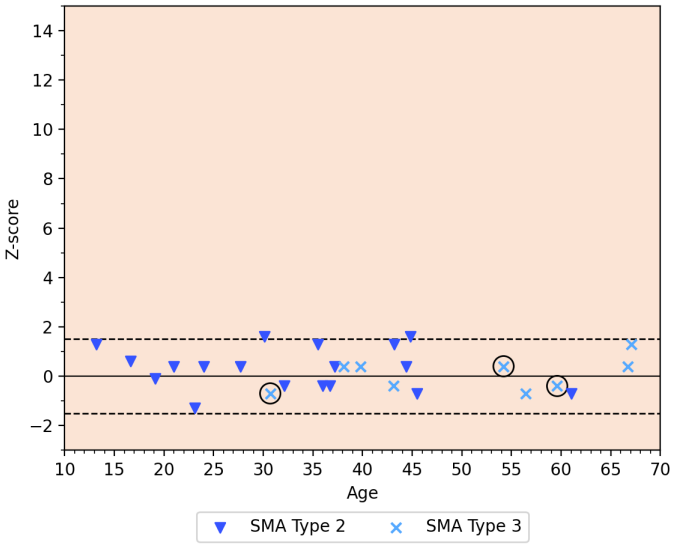
The three ambulant patients performed the test similarly to healthy subjects for discrete bites (median z-score -0.4), masticatory cycles (median z-score -0.2), swallows (median z-score 0.3) and time needed to finish the cracker (z-score 0.1).

Table 2. Z-scores of the TOMASS and 6 MMT for non-ambulant/ambulant patients, and non-ambulant patients with SMA type 2/3.

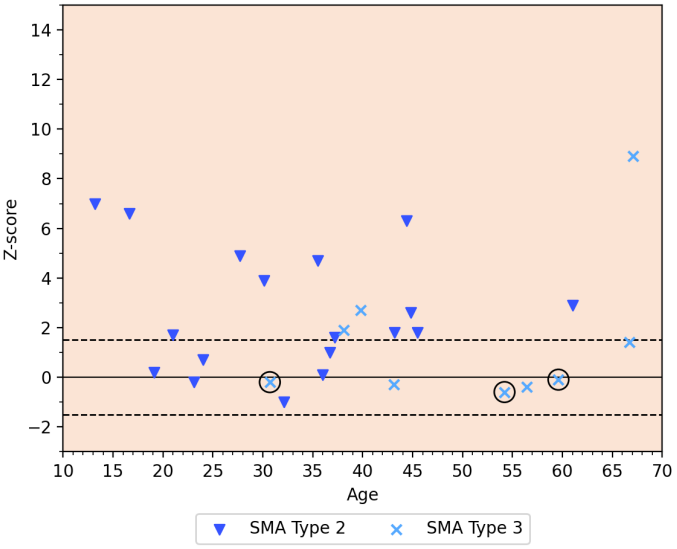
	TOMASS				6MMT	
	Discrete Bites	**Masticatory cycles**	**Swallows**	**Time**	**Masticatory cycles**	**Difference M1-M6**
SMA types 2 and 3/non-ambulant patients, median (range)	0.4 (-1.3 – 1.3)	1.8 (-1.0 – 8.9)	4.3 (0.3 – 13.7)	3.4 (-0.6 – 12.0)	-1.5 (-3.0 - 0.3)	-0.4 (-1.7 – 1.0)
SMA type 3/ ambulant patients, median (range)	-0.4 (-1.3 – 0.4)	-0.2 (-0.6 – 0.1)	0.3 (0)	0.1 (-0.1 – 0.5)	- 1.1 (-1.7 - - 1.1)	- 0.1 (-1.1 - 0.3).
SMA type 2 patients, median (range)	0.4 (-1.3 - 1.3)	1.8 (-1.0 – 7.0)	4.8 (0.3–13.7)	3.4 (-0.6 – 12.0)	-1.5 (-3.0 – 0)	-0.4 (-1.6 – 1.0)
SMA type 3 patients/ non-ambulant, median (range)	0.4 (-0.7 – 1.3)	1.7 (-0.4 – 8.9)	2.6 (0.3 – 7.0)	2.8 (-0.1 – 7.9)	-2.0 (-3.0 – 0.3)	0.2 (-1.7 – 0.4)

TOMASS = Test of Mastication and Swallowing Solids. 6MMT = 6-minutes mastication test.
Outcome measures of the TOMASS: discrete bites: number of bites needed to finish the standardized cracker; masticatory cycles: number of masticatory cycles (i.e. one cycle is the opening and closing of the jaws); swallows: number of observed movements of the thyroid cartilage; time: duration of the time needed to finish the cracker. Outcome measures 6MMT: masticatory cycles: total number of masticatory cycles; difference in masticatory cycles between minute 1 and minute 6.

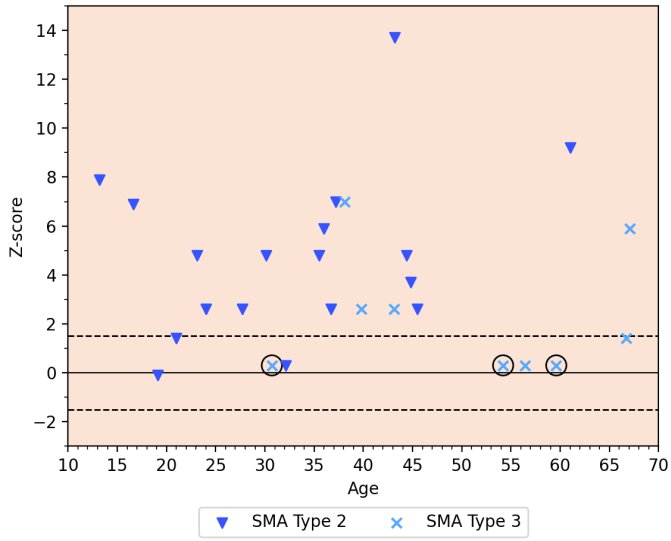
A. Discrete bites



B. Masticatory cycle



C. Swallow



D. Time

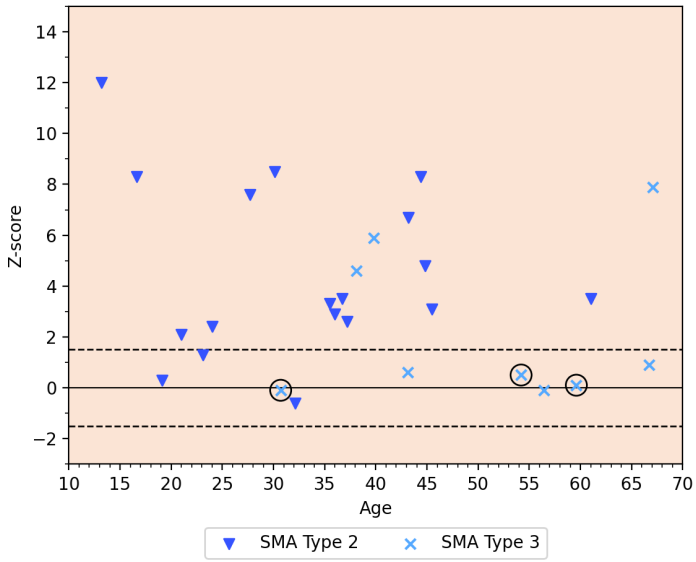


Figure 2. Z-scores of the TOMASS for patients with SMA type 2 and 3. A. Discrete bites, B. Masticatory cycles, C. Swallows, D. Time to finish the cracker

TOMASS = Test of Mastication and Swallowing Solids.
The circles refer to ambulant patients.

6-Minutes Mastication Test (6MMT)

The results of the 6MMT are summarized in Table 2. Z-scores of < -1.5 were considered normal. Five non-ambulant patients (21%) could not finish the 6MMT due to excessive fatigue of the masticatory muscles. One patient did not want to participate in the test because of jaw symptoms (Table 3). The rate of chewing tended to be slow (median z-score -1.5, range -3.8 – 0.3) and in four of 18 patients (22%) the difference in masticatory cycles between minute 1 and minute 6 was greater compared to healthy subjects (i.e. z-scores > -1.5). One of the three ambulant patients masticated at a slow pace (z-score -1.7). In all three patients, difference in masticatory cycles between minute 1 and minute 6 were similar to those in healthy subjects.

Table 3a. Z-sores of the TOMASS and 6 MMT for patients with SMA type 2.

			TOMASS				6MMT	
	Age	**SMA type**	**Discrete bites**	**Masticatory cycles**	**Swallows**	**Time**	**Masticatory cycles**	**Difference M1 – M6**
1	13	2	1.3	7.0	7.9	12.0	-2.2	-0.3
2	16	2	0.1	6.6	6.9	8.3	-1.8	-0.4
3	19	2	-0.4	0.5	0.3	0.9	-0.4	-0.1
4	21	2	0.4	1.7	1.4	2.1	-1.9	-1.3
5	23	2	-1.3	-0.2	4.8	1.3	-0.5	0.9
6	24	2	0.4	0.7	2.6	2.4	-3.0	[1]
7	27	2	0.4	4.9	2.6	7.6	-1.5	-1.5
8	30	2	0.4	3.9	4.8	8.5	-1.5	-1.0
9	32	2	-0.3	-1.0	0.3	-0.6	-1.3	-0.2
10	35	2	1.3	4.7	4.8	3.3	-0.8	-1.5
11	36	2	-0.4	0.1	5.9	2.9	-0.8	1.0
12	36	2	-0.4	1.0	2.6	3.5	-1.8	-1.6
13	37	2	0.4	1.6	7.0	2.6	0	-1.3
14	43	2	1.3	1.8	13.7	6.7	-1.0	-0.2
15	44	2	0.4	6.3	4.8	8.3	-3.0	[1]
16	44	2	0.4	2.6	3.7	4.8	-1.6	-0.1
17	45	2	-0.7	1.8	2.6	3.1	-3.0	[1]
18	61	2	-0.7	2.9	9.2	3.5	-0.9	-0.6

TOMASS = test of mastication and swallowing solids; 6MMT = 6 minutes mastication test; Difference M1 – M6 = difference between minute 1 and minute 6.

[1] patient could not finish the test.

The shaded areas are patients with posterior open bites.

Table 3b. Z-scores of the TOMASS and 6MMT for patients with SMA type 3.

			TOMASS				6MMT	
	Age	**SMA type**	**Discrete bites**	**Masticatory cycles**	**Swallows**	**Time**	**Masticatory cycles**	**Difference M1-M6**
19	**30**	**3**	**-1.3**	**-0.2**	**0.3**	**-0.1**	**-1.7**	**-0.1**
20	38	3	0.4	1.9	7.0	4.6	[2]	[2]
21	39	3	0.4	2.7	2.6	5.9	-3.0	[1]
22	43	3	-0.4	-0.3	2.6	0.6	-2.0	-1.7
23	**54**	**3**	**0.4**	**-0.6**	**0.3**	**0.5**	**-1.1**	**0.3**
24	56	3	-0.7	-0.4	0.3	-0.1	0.3	0.2
25	**59**	**3**	**-0.4**	**-0.1**	**0.3**	**0.1**	**-1.1**	**-1.1**
26	66	3	0.4	1.4	1.4	0.9	0.1	0.4
27	67	3	1.3	8.9	5.9	7.9	-3.0	[1]

TOMASS = test of mastication and swallowing solids; 6MMT = 6 minutes mastication test; Difference M1 – M6 = difference between minute 1 and minute 6
[1] patient could not finish the test, [2] test was not performed because of jaw-complaints
The bold data refer to ambulant patients
The shaded areas are patients with posterior open bites

Table 4 summarizes median VAS-scores for pain and fatigue directly after the 6MMT and 5 min later. SMA patients did not experience increased pain compared to healthy subjects directly after the test ($p = .531$), and 5 min. after the test ($p = .493$) . Patients experienced significantly more fatigue compared to healthy subjects, both directly after the test ($p < 0.001$) and 5 min after the test ($p = 0.003$) (Figure 3). The VAS scores for fatigue of the three ambulant patients were 2, 6 and 8 directly after the test; 5 min after the test they were 0, 6, 7.

Table 4. Median VAS-scores of the 6MMT, directly after the test (pain I, fatigue I) and 5 min after the test (pain II, fatigue II).

	Non-ambulant patients (n=24)	**Ambulant patients (n=3)**
VAS-score pain 1	1 (range 0 – 8)	1 (range 0 - 5)
VAS-score pain 2	0 (range 0 – 5)	0 (range 0 - 4)
VAS-score fatigue 1	7 (range 1 – 10)	6 (range 2 - 8)
VAS-score fatigue 2	2.5 (range 0 – 8)	6 (range 0 - 7)

The median VAS-score of healthy subjects (n=153) was for pain 1 (range 0 – 7) directly after the test (pain 1), and 2 (range 0 - 9) 5 min after the test (pain 2). For fatigue the median VAS-score was 0 (range 0 – 6) directly after the test (fatigue 1) and 1 (range 0 - 6) 5 min after the test (fatigue 2)

Fifteen of 23 non-ambulant patients (65%) had rhythmical jaw movements during mastication, 4 patients (17%) showed variable movements, and 4 patients (17%) had arrhythmical jaw movements. Magnitude of jaw movements was qualified as normal in 4 patients (17%), and small in 19 patients (83%). There were no patients with large jaw movements. The three ambulant patients had rhythmical jaw movements of normal magnitude.

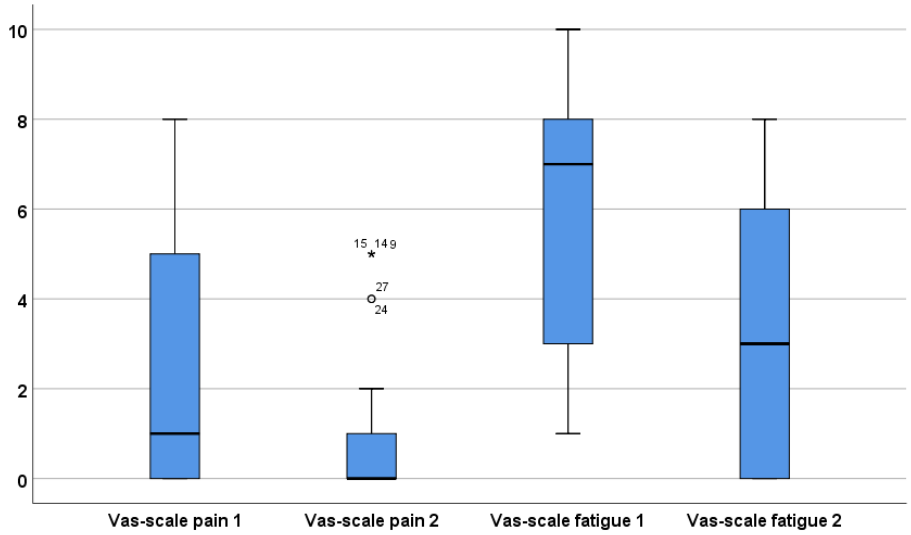


Figure 3. VAS-scales for pain and fatigue after the 6-min mastication test.

Distribution of the data of the VAS-scales (0 = no complaints, 10 = severe complaints) for pain directly after the test (pain 1), pain 5 minutes after the test (pain 2), fatigue directly after the test (fatigue 1), and fatigue 5 minutes after the test (fatigue 2).

Relation between active maximum mouth opening and results of the TOMASS

Univariate regression analysis showed that aMMO significantly contributed to the time needed to finish a standardized cracker ($F(1,25) = 19.28$, $p < 0.001$) (Figure 4). The mean effect of an increase of 1 mm in aMMO was a 3% decrease in time needed to finish the cracker (95% CI 1.60 to 4.36). Overall, aMMO explained over 40% of the variation in the log TOMASS total time (adjusted $R2 = 0.413$).

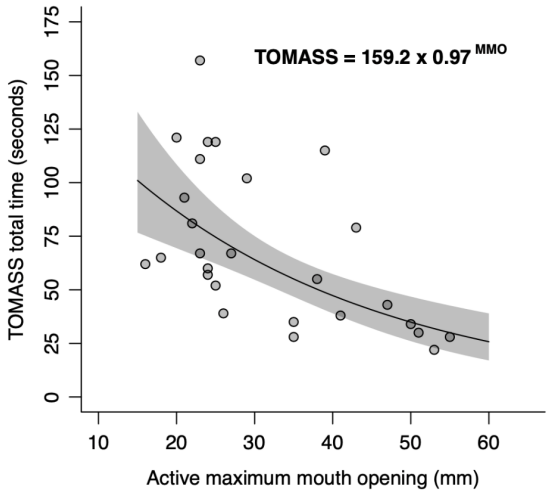


Figure 4. Linear regression between the log (TOMASS total time) and active maximal mouth opening. TOMASS: test of mastication and swallowing solids.

Relation between questionnaire and mastication test results

The association between 'do you adapt food?' and efficiency of mastication was significant ($p < 0.001$). All six patients who did not adapt food (for instance by cutting into pieces, pureeing it or avoiding hard foods) had normal efficiency of mastication (z-scores < 1.5). There was also a significant association between 'do you experience difficulty with chewing?' and efficiency of mastication ($p = 0.001$). Not all patients were aware of mastication problems because three of 11 patients (27%) reported no difficulty chewing, but their efficiency of mastication was abnormal.

Muscle ultrasound of bulbar muscles

Masticatory muscles frequently showed increased echogenicity with a moth-eaten pattern in non-ambulant and ambulant patients (Figure 1). The masseter muscle was most often affected (85% of the patients), followed by the temporalis muscle (63% of the patients). Assessments of the tongue muscles were possible in 20 of 27 patients. Ten patients had increased echogenicity with a moth-eaten pattern and 9 patients increased echogenicity of the tongue muscles. In seven of 27 patients (26%) the transducer could not be placed on the tongue as a result of reduced mouth opening. The echogenicity of the tongue muscles could not be determined in these patients.

Discussion

This study shows that mastication in non-ambulant patients with SMA types 2 and 3 is characterized by a combination of inefficient mastication, reduced endurance, fatigue during and after mastication, and altered oral anatomy (i.e. reduced maximum mouth opening and dental malocclusion). The three ambulant patients showed normal masticatory efficiency, but also demonstrated reduced endurance or fatigue.

Previous studies have shown brainstem alpha-motor neuron involvement with a caudal-to-rostral gradient in SMA. (4,5,6). Granger et al. were the first to report reduced bite force, jaw movements and endurance in 15 patients with SMA (7). These early observations were corroborated by a small number of studies assessing maximum mouth opening, jaw mobility and bite force (8,9,10). Reduced maximum mouth opening is very common among patients with SMA type 2 (8,9,10,29) and probably progresses over time from an early age. MR images show that this complication is caused by the preferential fatty degeneration and atrophy of the lateral pterygoid muscle, which not only mediates mouth opening, but also allows the horizontal masticatory movements that increase masticatory efficiency (30).

The first important observation of our study is that non-ambulant patients require more masticatory cycles and a prolonged time before they are ready to swallow. Although this may be attributable to weakness of the masticatory muscles, reduced mobility of the jaws (i.e. horizontal mastication movements) probably has a greater impact. Dental malocclusion, which is related to weak masticatory and facial muscles may further aggravate masticatory inefficiency (31).

A second important observation was reduced endurance of continuous mastication. Limited endurance (i.e. 'fatigability') is a specific feature of SMA during repetitive muscle contractions and may be at least partially caused by abnormal neuromuscular junction function (2,21,24,32,33).

Ultrasound showed increased echogenicity of masseter and temporalis muscles both in non-ambulant and ambulant patients, suggesting widespread abnormalities in bulbar muscles and complementing a previous MRI study (10). It is the first time that muscle ultrasound of bulbar muscles is performed in SMA patients with documented mastication and/or swallowing problems. The ultrasound images were assessed qualitatively. The specific structure of the muscles previously described for skeletal muscles of patients with SMA, was also present in the bulbar muscles of the patients in our study (26,34). Despite abnormalities in bulbar muscle structure, ambulant patients still managed to chew efficiently, suggesting functional reserve capacity of muscle

force. This is illustrated by the fact that masticatory performance did not differ between patients with SMA and healthy subjects, although a significantly lower maximum voluntary bite force has been reported in this patient group (9). This phenomenon of a changing muscle structure in combination with maintenance of relatively efficient mastication has also been observed in patients with Duchenne muscular dystrophy (35).

Problems with mastication have a profound impact on the quality of life of patients with SMA. Despite the frequent food adaptations as reflected in the functional oral intake scale (Table 1) patients needed more time to process food compared to healthy subjects. This probably also affects the social function of eating, because patients need to stay focused on the task of chewing, while avoiding conversations during mealtime in order to thoroughly prepare the food for safe swallowing.

When comparing questionnaire and clinical test results we found underreporting of masticatory problems. A considerable number of patients had inefficient mastication but did not report symptoms. This probably reflects the continuous adaptations to the consequences of progressive bulbar problems. It indicates that it is not sufficient to use only a questionnaire to detect mastication problems. Questionnaires combined with aMMO, TOMASS and 6MMT provide quantitative and qualitative information about masticatory performance and can be used in clinical practice. Oral muscle ultrasound is supplemental to the clinical assessment of mastication and may support the explanation of the change in mastication function.

In order to prevent loss of function of masticatory muscles due to disuse, patients are probably best advised to continue to use food they can still chew and swallow safely. Obviously, patients with severe mastication problems will need to adapt the ratio between chewable food and soft food. Although there is little evidence that stretching exercises reverse or delay limitations of aMMO, some patients claimed that stretching stabilized aMMO (36). Given the major effect of aMMO on chewing efficiency, the effects of stretching need to be studied in more detail.

This study has certain limitations. First of all, the sample size, in particular of ambulant patients was small. This can be attributed to the inclusion criterion of having bulbar problems. Although the participation of more ambulant patients would have allowed more definite conclusions, a previous study showed that aMMO in ambulant patients remains within the normal range (9). This suggests that mastication problems (masticatory inefficiency) are less likely to occur in ambulant patients. Another limitation is that 'number

of swallows' (TOMASS) were determined by visual observations and not by objective methods such as sEMG.

Conclusion

Mastication problems in patients with SMA types 2 and 3 are characterized by inefficiency, reduced endurance and fatigue, probably caused by masticatory muscle changes that can be detected by ultrasound. Not all patients were aware of their mastication problems. In the future, it would probably be advisable to apply a combination of quantitative and qualitative mastication tests in addition to a questionnaire, to test masticatory function in non-ambulant patients with SMA. Interventions should aim to maintain jaw mobility, dental occlusion and endurance of mastication.

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Chapter 4

Swallowing problems in spinal muscular atrophy types 2 and 3: a clinical, videofluoroscopic and ultrasound study

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Abstract

Background

Spinal muscular atrophy (SMA) is a hereditary motor neuron disorder, characterized by the degeneration of motor neurons and progressive muscle weakness. There is a large variability of disease severity, reflected by the classification of SMA types 1–4.

Objective

The aim of this cross-sectional study was to determine the nature of swallowing problems and underlying mechanisms in patients with SMA types 2 and 3, and the relationship between swallowing and mastication problems.

Methods

We enrolled patients (aged 13–67 years) with self-reported swallowing and/or mastication problems. We used a questionnaire, the functional oral intake scale, clinical tests (dysphagia limit, and timed test swallowing, the test of mastication and swallowing solids), a videofluoroscopic swallowing study (VFSS), and muscle ultrasound of the bulbar muscles (i.e. digastric, geniohyoid and tongue muscles).

Results

Non-ambulant patients (n = 24) had a reduced dysphagia limit (median 13 ml (3–45), and a swallowing rate at the limit of normal (median 10 ml/sec (range 4–25 ml). VFSS revealed abnormal piecemeal deglutition and pharyngeal residue. We found pharyngo-oral regurgitation in fourteen patients (58%), i.e. they transported the bolus from the hypopharynx back into the oral cavity and re-swallowed it. Six patients (25%) demonstrated impaired swallowing safety (i.e. penetration aspiration scale >3). Muscle ultrasound revealed an abnormal muscle structure of the submental and tongue muscles. Ambulant patients (n = 3), had a normal dysphagia limit and swallowing rate, but VFSS showed pharyngeal residue, and muscle ultrasound demonstrated an abnormal echogenicity of the tongue. Swallowing problems were associated with mastication problems (p = 0.001).

Introduction

Hereditary proximal spinal muscular atrophy (SMA) is caused by a loss of the function of Survival Motor Neuron 1 (SMN1) gene (1). The disorder is characterized by alpha-motor neuron degeneration, abnormalities of neuromuscular junction anatomy and function, muscle atrophy and weakness. SMA is one of the most common hereditary neuromuscular disorders, with an incidence of approximately 1 in 10,000 live births (2). The wide severity spectrum is reflected by the clinical classification of SMA that distinguishes types 1, 2, 3, and 4 around the time of diagnosis, based on age at onset and highest of two achieved motor milestones, i.e. independent sitting or walking (3–5). Patients with SMA type 1 may acquire head control or learn to roll but will never learn to sit independently (i.e. 'non-sitters'); patients with SMA type 2 achieve independent sitting, but not walking (i.e. 'sitters'); patients with SMA type 3 learn to walk independently (i.e. 'walkers'). SMA type 4 is characterized by adult onset and relative mild weakness. Since SMA is a progressive disorder, patients often lose acquired motor skills later in life. Therefore, the term 'non-sitters' may refer to both patients with SMA type 1 and patients with SMA type 2 who have lost the ability to sit independently, and 'non-walkers' to patients with SMA type 2 and those with type 3 who lost the ability to walk (5).

The most important feature of SMA is muscle weakness, which is more pronounced in legs than arms and also affects axial, intercostal and bulbar muscles (such as submental and tongue muscles). Patients with SMA frequently report issues such as impaired jaw function, fatigue when chewing, difficulty swallowing solid food and choking (6–11). Swallowing problems are accompanied by an increased risk of respiratory complications and malnutrition, but studies investigating the nature of swallowing problems and underlying disturbed mechanisms in SMA, are sparse. Clinical observational studies reported reduced active maximum mouth opening (aMMO), caused by fatty degeneration of the bulbar muscles, especially the lateral pterygoid muscle (responsible for opening the jaw) (12–14). Videofluoroscopic swallowing study (VFSS) revealed piecemeal deglutition (i.e. swallowing the bolus in small successive particles) and pharyngeal residue in children with SMA type 2 (15). Until now, swallowing problems have not been studied in a larger number of patients with SMA, nor using a combination of techniques. In a previous study we examined the mastication function in patients with SMA type 2 and 3 (16). In the present study, the swallowing function was investigated in the same patients. This study aimed to contribute to our understanding of the nature of swallowing problems and underlying mechanisms, in patients with

SMA types 2 and 3. The second aim was to investigate the relationship between swallowing and mastication.

METHODS

Participants

Between August 2018 and 2019 patients of the Dutch SMA registry (i.e. patients enrolled in our ongoing population-based cohort study) with SMA type 2 and 3 were invited to participate (17, 18). We included 27 patients aged 13 years and older. Those patients, who mentioned mastication and/or swallowing problems (i.e. fatigue or difficulty with chewing; feeling of food sticking in the throat; coughing when swallowing liquids or solid foods; mealtimes longer than 30 minutes; the need for diet modification; tube feeding required) were enrolled (8). The study protocol consisted of a single hospital visit. Both the mastication and swallowing function were investigated. The results of the mastication function were published in a previous article (16). At the time of enrollment, patients did not have access to SMN-augmenting therapies such as nusinersen or risdiplam. Six patients used pyridostigmine (i.e. a cholinesterase inhibitor that improves the strength of the muscles) (19, 20). In order to prevent this drug from influencing the swallowing function, patients were asked not to take it on the day of the study.

The Medical Research and Ethics Committee (METC) of the University Medical Center Utrecht decided to only include patients with self- reported swallowing and/or mastication symptoms, and approved the study protocol according to Dutch legislation on clinical studies (METC 17–718). Informed consent was obtained from the patients, or in the case of patients younger than 16 years, from both patients and parents.

Study design

Swallowing was assessed, using a combination of a self-report questionnaire, dysphagia limit (DL), timed test swallowing (TTS), VFSS and muscle ultrasound of the digastric, geniohyoid and tongue muscles. Two experienced speech-language therapists (SLTs) (AMBH and LEH) performed the assessments.

Questionnaire and clinical scales

We used the questionnaire 'Diagnostic List of Dysphagia and Dysarthria in (pediatric) patients with neuromuscular Diseases (DDD(p)NMD)'. The dichotomous questions of this questionnaire focus on masticatory, swallowing and jaw issues and consequences for mealtime duration, food adaptations,

weight, and the occurrence and frequency of respi- ratory infections. This questionnaire was originally developed by a group of SLTs involved in the care of dysphagia in neuromuscular diseases with the aim of identifying feeding and swallowing problems (21). The questionnaire overlaps with those used in other studies about feeding and swallowing problems in patients with SMA (6, 7). It has been used previously in patients with SMA (8), and test-retest reliability was sufficient (n = 14, ICC = 0.94. (CI 0.80–0.98). We used the functional oral intake scale (FOIS). This is an ordinal scale, reflecting the functional oral intake of patients, with scores ranging from 1 'nothing by mouth' to 7' total oral diet with no restrictions' (22).

Dysphagia limit (DL)

The aim of the DL test is to establish the maximum volume of water that can be swallowed in a single effort. It determines the presence and extent of piecemeal deglutition. This test has been validated with 75 healthy participants and 149 neurological patients with a swallowing disorder, and also 28 neurological patients without a swallowing disorder. No healthy participant had a dysphagia limit of <20 ml (23). Reliability has not been explicitly investigated, but the observations are unambiguous due to the use of a syringe for the correct volume, and auscultation to determine the number of swallows. We offered patients 10 ml of tap water in a cup and asked them to swallow this in a single swallow. If the patient succeeded, we increased the bolus volume until the patient needed to swallow more than once. If the patient could not swallow 10 ml in one swallow, bolus volumes were gradually reduced. The largest volume swallowed in one effort was documented. We used cervical auscultation to assess the number of swallow sounds. The diagnostic value of 20 ml was used as the boundary between normal/abnormal volumes swallowed in a single effort (23).

Timed Test of Swallowing (TTS)

The aim of the TTS is to measure swallowing speed. Validation of this test with 150 ml water was performed, with 101 healthy participants, and 181 healthy participants by Nathadwarawala et al (1992) and Hughes et al (1996). No participant (aged <70 years) had a swallowing speed lower than 10 ml/sec. From 19 patients with a swallowing disorder, 14 patients had a swallowing speed <10 ml/sec. Intra and inter reliability of the test was sufficient.

We offered patients 100 ml of tap water. We instructed the patient to drink this as fast as possible, but safely', and to say 'yes' when finished. The patient was videotaped laterally to determine the number of swallows and total time

needed to complete swallowing 100 ml (time in seconds from the moment the first water passed the lower lip, until the patient indicated that he/she was finished). Not all patients were able to handle the cup independently (n = 12), in which case their results were excluded from analysis. We used the diagnostic value of 10 ml/sec as the boundary between normal and abnormal swallowing speed (24–26).

Videofluoroscopic Swallowing Study (VFSS)

VFFS was performed with a Philips Multi Diagnost Eleva C-arm, and VFSS images were collected in lateral view at 15 pulses per second, and pictures were stored in the picture archiving and communication system (PACS). Ambulant patients sat on a chair with a backrest adjustable for height to ensure an optimal upright position. Non-ambulant patients sat in their wheelchairs, meeting their individual needs. We used an iodine-containing nonionic contrast material. Three different consistencies were offered, and patients swallowed three boluses of each consistency. They started with IDDSI level 0, presented as a 10 ml sip in a cup. IDDSI level 3 which was thickened with a standardized amount of locust bean gum, checked on consistency, and presented on a dessert spoon (10 ml). The soft pieces bread (2 × 2 cm) of IDDSI level 7 were coated with contrast material and presented piece by piece (27).

We duplicated recordings of each bolus to analyze images of the VFSS, blinded for patient characteristics, consistency offered, and order of bolus presentation. Two SLTs (AMBH and LEH) scored the recordings together, in random order, on the following aspects: (a) number of swallows per bolus (i.e. passage of a bolus through the oesophagus), (b) pharyngeal residue with the bolus residue scale (BRS) (29), (c) pharyngo-oral regurgitation, and (d) penetration/aspiration with the penetration aspiration scale (PAS) (30). Any difference in ratings were repeated and debated until consensus was achieved.

We determined the limit of a usual number of swallows for the standardized boluses, applying reference values from healthy participants. Comfortable sip volumes of thin liquid (IDDSI level 0) in healthy adults range from 11–14 ml. Twenty percent of healthy adults perform a 'cleanup swallow' (i.e. a second swallow) (28). Therefore, for a bolus of 10 ml thin liquid, we considered three or more swallows as abnormal. The mean swallow volume of moderately thick liquid (IDDSI level 3) in healthy adults was 4.9 ml (95%CI 4.4–5.4) (28). Therefore, two or three swallows (a cleanup swallow included) were considered normal, and four or more swallows as abnormal. For the pieces of bread (IDDSI level 7), no reference values were available; we therefore used the reference values of moderately thick consistencies (28). Swallowing

efficiency was evaluated with the BRS. The scale classifies pharyngeal residue in the valleculae, piriform sinuses and/or posterior pharyngeal wall, ranging from 1 = no residue to 6 = residue in valleculae, on the posterior pharyngeal wall and in pyriform sinuses. A higher BRS score is associated with a higher risk of aspiration (29). We scored BRS regardless of pre-swallow pharyngeal residue. BRS was captured from the frame of 'swallow rest', where the piriform sinuses were at their lowest position after swallowing, as part of post swallow pharyngeal relaxation. In this study it was not possible to quantify the volume of residue because of the markedly dilated hypopharynx in several patients. In addition, in some patients it was impossible to make fully lateral images due to severe scoliosis.

In some of the first few patients, we unexpectedly observed an exceptional phenomenon, best described as 'pharyngo-oral regurgitation'. Instead of moving the bolus into the oesophagus, they transported it from the hypopharynx back into the oral cavity and re-swallowed it. The phenomenon occurred when the bolus had been partially swallowed and pharyngeal residue was observed. This residue was transported from the pharynx back into the oral cavity and re-swallowed We documented whether this phenomenon was present in each subsequent patient.

We used the PAS to determine by which extend material entered the airway, and by whether the material entering the airway was ejected. The 8-point scale ranges from 1 (no material entering the airway) to 8 (material enters the airway, passes the vocal folds, and no effort is made to eject) (30). PAS scores >3 were considered as impaired swallowing safety. For PAS scores >2, we involved the radiologist. For these cases, the radiologist (RAJN) and a SLT (AMBH) independently scored the PAS. Differences in scores were resolved by consensus.

For interrater reliability, 30% of the images (70 out of 240 randomly chosen boluses) were rated independently by the raters. For interrater- reliability, the agreement of the number of swallows was analyzed with a two-way random effect intraclass correlation coefficient (ICC). ICC demonstrated excellent inter-reliability for the number of swallows (ICC r = 0.93, CI 0.88–0.95). Cohen's kappa was almost perfect for pharyngo-oral regurgitation ($\kappa = 0.81$), substantial for pharyngeal residue ($\kappa = 0.63$) and moderate for penetration-aspiration ($\kappa = 0.43$).

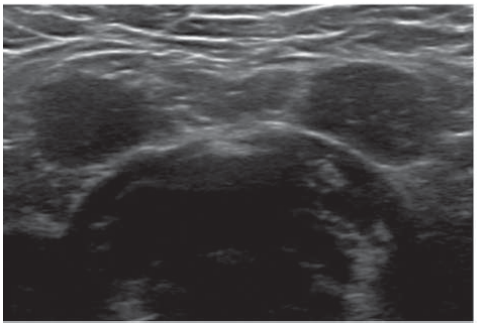
Muscle ultrasound

We performed muscle ultrasound to visualize the structure of submental muscles (i.e. digastric, and geniohyoid muscles) and tongue muscles (31–33). We used an Affiniti 70 Philips Ultrasound System (Philips, the Netherlands) with a 12-5

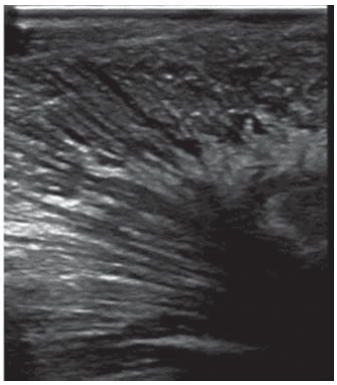
MHz transducer (Figure 1). During examination head and neck of the patients were in a neutral position. A broad- band linear intraoperative (so-called hockey stick) 14-5 MHz transducer was used for the tongue (Figure 1). The patient opened his/her mouth, and the transducer was placed on the anterior part of the tongue. Data were stored as DICOM images in PACS. We scored images qualitatively, based on consensus (LEH and her colleague SLT, experienced in interpreting muscle ultrasound images) either (1). 'normal structure and echogenicity', (2). 'increased echogenicity with a moth-eaten pattern' or (3). 'increased echogenicity' (Figure 2) (31, 33, 34). Raters did not have access to patient characteristics or results of other assessments of the study.

Figure 1. Muscle ultrasound of the submental and tongue muscles. A 12-5 MHz transducer was used for the submental muscles (i.e. digastric, and geniohyoid muscles) (left); a 14-5 MHz transducer (hockey stick) was used for the tongue muscles (right).

Score 1, normal echogenicity

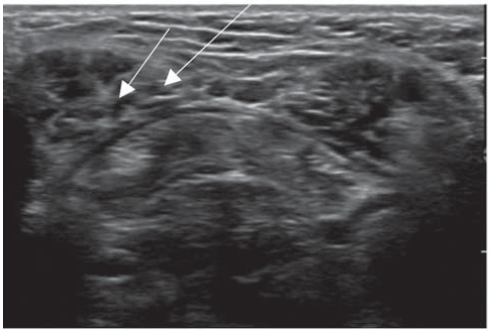


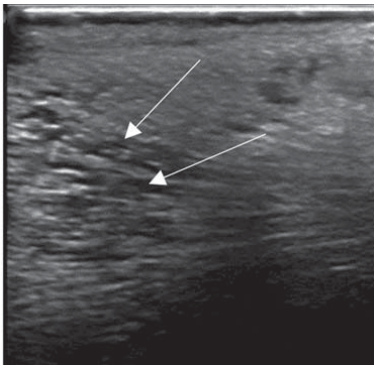
Submental muscles



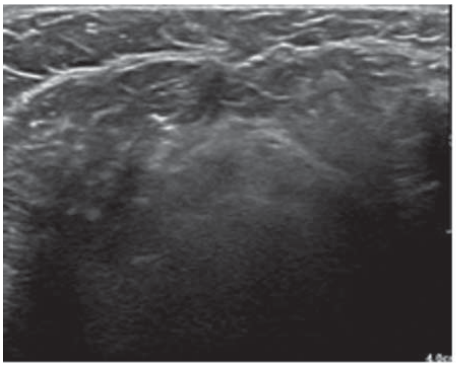
Tongue muscles

Score 2, moth eaten pattern (arrows) and increased echogenicity





Score 3, increased echogenicity



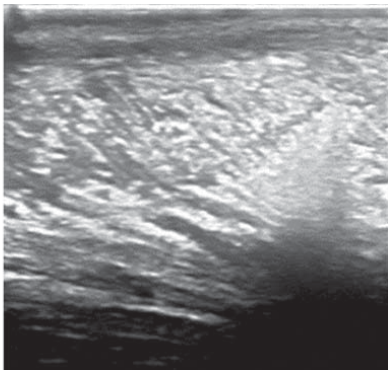


Figure 2. Muscle ultrasound images of the submental and tongue muscles, with normal echogenicity (score 1), increased echogenicity with an inhomogeneous, moth-eaten pattern (arrows) (score 2), and increased echogenicity, where muscle outline fade and disappear (score 3).

Relation between swallowing and mastication

To investigate the relation between swallowing and mastication problems, we used the DL test, and the test of mastication and swallowing solids (TOMASS) (35), described in a previous study (16). For this test the patient eats a standardized cracker as fast as possible. We used the total time (TT) in seconds needed to finish the cracker as an outcome measure of efficiency of mastication.

Statistical analysis

We used descriptive statistics for patient characteristics, data of the questionnaire, DL, TTS, VFSS and muscle ultrasound (median (range), n (%), or median (IQR). The results of the questionnaire, clinical and instrumental tests were stratified according to the level of motor function: non-ambulant versus ambulant patients.

For analysis, we used the highest (i.e. worst) scores of the BRS, PAS and the number of swallows for each bolus for analysis. Associations between the PAS scores (dichotomized </≥3) for IDDSI level 0 and questionnaire's items were analyzed with a Fisher exact test for categorical data. For the relation between swallowing problems and mastication problems we used the DL (ml), and the TOMASS, (total time (sec) needed to finish the cracker), and calculated a Spearman's correlation.

A p-value of <0.05 was considered as significant. Data were analyzed using SPSS 26 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

Table 1 summarizes patient characteristics.

Table 1. Patient characteristics

	SMA type 2(n=18)	SMA type 3(n=9)
Sex (F: M)	13:5	6:3
Age in years, median (range)	32 (13 – 61)	54 (30– 67)
Non-ambulant: Ambulant	18:0	6:3
Current respiratory status: No respiratory management, n (%) Non-invasive ventilation [a], n (%) Invasive ventilation [b], n (%)	 14 (78) 4 (22)	 6 (67) 2 (22) 1 (11)
aMMO (in mm) non-ambulant patients, median (range)	24 (16 – 53)	37 (21 – 43)
aMMO (in mm) ambulant patients, median (range)	n/a [c]	51 (50 – 55)
FOIS, median (range)	5 (2 –7)	5 (5 – 7)

Abbreviations: SMA, spinal muscular atrophy; F, female; M, male; n, number of patients.
a Non-invasive ventilation: ventilation support provided via a face mask. Patients used non-invasive ventilation during the night. b Invasive ventilation: positive air pressure support provided via a tracheostomy. The patient used invasive ventilation, with inspiratory and expiratory pressure during day and night; aMMO, active maximum mouth opening; n/a: not applicable. c Patients with SMA type 2 are non-ambulant; FOIS, functional oral intake scale.

Questionnaire

The most common swallowing problem of the non- ambulant patients (n = 24) was difficulty swallowing solid food (92%). The feeling of food sticking in the throat was reported by 18 of 24 patients (75%). None of the patients reported problems swallowing liquids exclusively. Impaired swallowing safety was captured by 'choking more than once a day', 'coughing with solid foods', and 'coughing with liquids'. These complaints were reported by, respectively, 25%, 29% and 29% of the patients. Twenty-one patients (88%) managed swallowing and/or mastication problems by dietary modification (i.e. pureeing solid food or cutting it into small pieces or avoiding certain kinds of food). Half of the patients reported mealtimes longer than 30 minutes (54%).

Two of three ambulant patients reported the feeling of food sticking in the throat. These patients did not mention other swallowing problems, nor did they report modified diets or mealtimes >30 minutes.

Clinical swallowing tests

Seventeen non-ambulant patients (71%) had an abnormal DL (i.e. <20 ml). The median DL was 13 ml (3–45). The TTS of non-ambulant patients was at the lower limit of normal, with a median swallowing speed of 10 ml/sec (range 4–25 ml). Eight of 12 patients (67%) had a TTS of >10 ml, and four patients (33%) <10 ml.

The ambulant patients had a median DL of 40 ml (range 20–45) and a TTS of 17 ml/sec (range 14–20).

Videofluoroscopic swallowing study

The results of VFSS are presented in Table 2. Abnormal piecemeal deglutition (i.e. swallowing the standardized bolus in more swallows than expected) was observed in non-ambulant patients with thin liquid (79%), moderately thick liquid (33%) and soft solid food (33%). In most non-ambulant patients, there was pharyngeal residue following ingestion of thin liquid (79%), moderately thick liquid (88%) and soft solid food (22%). A striking finding was pharyngo-oral regurgitation (i.e. transporting the bolus from the hypopharynx back in the oral cavity and swallowing again) in 14 non- ambulant patients (58%), almost all on IDDSI level 7. Five of these patients had pharyngo-oral regurgitation with more than one consistency. Impaired swallowing safety (i.e. Pas >3) was observed in 6 non-ambulant patients (25%) with SMA type 2. Three of them had laryngeal penetration and three patients had aspiration. In five out of six patients, penetrated or aspirated material was not ejected from the airway. Two of these six non-ambulant patients aspirated also on pharyngeal residue of the previous boluses when swallowing soft solid food (Table 2).

Ambulant patients demonstrated no abnormal piecemeal deglutition, but two of three patients had residue in the valleculae or pyriform sinus. There was no laryngeal penetration, aspiration or pharyngo-oral regurgitation in the ambulant patients (Table 2).

Table 2a. Results of the VFSS of patients with SMA type 2 (n=18) and 3 (n=9)

	IDDSI level 0		IDDSI level 3		IDDSI level 6	
	SMA type 2	**SMA type 3**	**SMA type 2**	**SMA type 3**	**SMA type 2***	**SMA type 3**
I. Number of swallows on a standardized bolus, median, (IQR)	3 (1)	2 (3)	3 (1)	2 (1)	3 (2)	1 (2)
II. Bolus residue scale, median, (IQR)	6 (3)	2 (3)	6 (2)	2 (4)	3 (1)	2 (2)
1. no residue, n (%)	1 (6)	3 (33)[a]	1 (6)	4 (44)[b]	3 (18)	4 (44)[c]
2. residue in valleculae, n (%)		2 (22)[a]	1 (6)	2 (22)	1 (6)	2 (22)
3. residue in posterior pharyngeal wall or in piriform sinus, n (%)	4 (22)	2 (22)[a]	2 (11)	1 (11)[a]	9 (53)	2 (22)
4. residue in valleculae and posterior pharyngeal wall or piriform sinus, n (%)	4 (22)	1 (11)	2 (11)	--	2 (12)	1 (11)
5. residue in the posterior pharyngeal wall and piriform sinus, n (%)	--	--	1 (6)	--	--	--
6. residue in valleculae and posterior pharyngeal wall and piriform sinus, n (%)	9 (50)	1 (11)	11 (61)	2 (22)	2 (12)	--
III. Pharyngo-oral regurgitation, n (%)	2 (11)	1 (11)	4 (22)	1 (11)	10 (59)	2 (22)

Number of swallows (I), bolus residue scale (II) pharyngo-oral regurgitation (III), when swallowing a standardized bolus for IDDSI level 0 = thin liquid, IDDSI level 3 = moderately thick liquid, IDDSI level 6 = soft & bite-sized food.

Table 2b. Results of the VFSS of patients with SMA type 2 (n=18) and 3 (n=9)

	IDDSI level 0		IDDSI level 3		IDDSI level 6	
	SMA type 2	**SMA type 3**	**SMA type 2**	**SMA type 3**	**SMA type 2***	**SMA type 3**
IV. Penetration-aspiration scale Rosenbek, median (IQR)	2 (3)	1 (0)	1 (1)	1 (0)	1 (0)	1 (0)
1. material does not enter the airway, n (%)	6 (33)	8 (89)[c]	13 (72)	9 (100)[c]	15 (88)	9 (100)[c]
2. material enters airway, above vocal folds and is ejected, n (%)	6 (33)	1 (11)	2 (11)	--	1 (6)	--
3. material enters the airway, above vocal folds, not ejected, n (%)	2 (11)	--	--	--	--	--
4. material enters the airway, contacts vocal folds, ejected, n (%)		--	1 (6)	--	--	--

Table 2b. Continued

	IDDSI level 0		IDDSI level 3		IDDSI level 6	
	SMA type 2	**SMA type 3**	**SMA type 2**	**SMA type 3**	**SMA type 2***	**SMA type 3**
5. material enters the airway, contacts vocal folds, not ejected, n (%)	2 (11)	--	--	--	[d]	--
6. material enters the airway, below vocal folds, ejected, n (%)	--	--	--	--	--	--
7. material enters the airway, below vocal folds, not ejected despite effort, n (%)	--	--	--	--	--	--
8. material enters the airway, below vocal folds, no effort made to eject, n (%)	2 (11)	--	2 (11)	--	[d]	--

Penetration-aspiration scale (IV) when swallowing a standardized bolus for IDDSI level 0 = thin liquid, IDDSI level 3 = moderately thick liquid, IDDSI level 6 = soft & bite-sized food.
Values in Table 2a and 2b are expressed as median (Inter Quartile Range), or n (%). VFSS: videofluoroscopic swallowing study. IDDSI: International Dysphagia Diet Initiative. Number of swallows of a standardized bolus: the number of swallows needed to swallow 10 ml IDDSI level 0 (thin liquid), 10 ml IDDSI level 3 (moderately thick) and 2 x 2 x 0.5 cm IDDSI level 6 (soft and bite sized). Bolus residue scale: scale to classify pharyngeal residue in the valleculae, piriform sinuses and/or posterior pharyngeal wall. Pharyngo-oral regurgitation: the transport of the bolus from the hypo-pharynx back into the oral cavity again, before it is re-swallowed.
Penetration-aspiration scale Rosenbek: scale to determine by which extend material enters the airway, and by whether the material entering the airway is ejected. Table cells with -- refer to: no patients with this score. *1 missing. a 1 ambulant patient, b 2 ambulant patients, c 3 ambulant patients d 1 non-ambulant patient aspirated on pharyngeal residue of the previous bolus.

Muscle ultrasound

Eighteen non-ambulant patients (75%) had increased echogenicity of the submental muscles. The ultrasound had an inhomogeneous moth-eaten pattern. The echogenicity of the tongue was increased in seventeen patients (71%), and in nine of these, the ultrasound revealed a moth-eaten pattern. In seven patients, the echogenicity of the tongue could not be determined, as it was impossible to place the transducer on the tongue, due to a limited maximum mouth opening.

Ambulant patients had normal echogenicity of the submental muscles, and two of three patients had increased echogenicity of the tongue (one with a moth-eaten pattern).

Relation between VFSS and the questionnaire

Pas scores ≥ 3 were significantly associated with 'daily use of antibiotics' (p = 0.011) and 'coughing with liquids (p = 0.001) but was not significantly associated with 'choking' (p = 0.588).

Relation between swallowing and mastication problems

The correlation between swallowing and mastication problems was significant (rs = −0.62, p = 0.001). An increase in the time needed to finish a standardized cracker was associated with a decrease of DL (Figure 3).

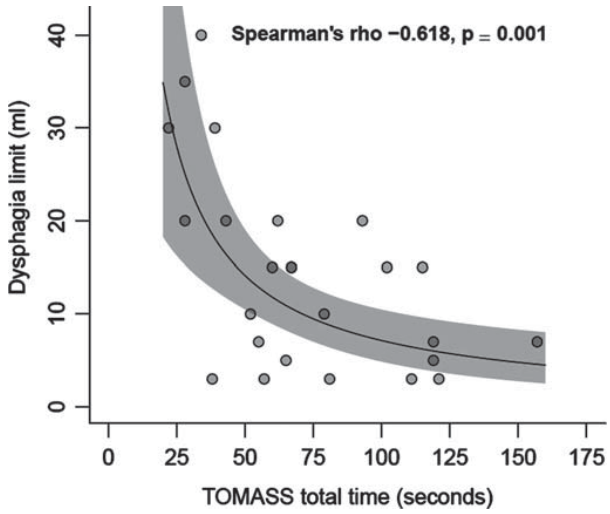


Figure 3. Correlation between swallowing and mastication problems, using dysphagia limit (ml) and TOMASS.

Dysphagia limit: the maximum volume of water that can be swallowed in a single effort. TOMASS: test of mastication and swallowing solids (total time in sec).

Discussion

This study provides insight into characteristics of swallowing problems in adolescent and adult patients with SMA types 2 and 3. Almost all non-ambulant patients swallowed inefficiently as reflected by abnormal piecemeal deglutition, pharyngeal residue, and pharyngo-oral regurgitation after stagnation in the hypopharynx. Only patients with SMA type 2 had impaired swallowing safety. Ambulant patients demonstrated no piecemeal deglutition or pharyngo-oral regurgitation but did have pharyngeal residue

after swallowing. We cannot exclude that patients with SMA type 3 will eventually develop significant symptoms of swallowing problems later in life. Investigation of more and older patients will probably clarify this.

Our results indicate that pharyngeal residue is common across the severity spectrum of SMA type 2 and even type 3, confirming the previous study in 6 pediatric patients with SMA type 2 (15). Studies in healthy participants, found minimal pharyngeal residue and a significant association between pharyngeal residue and indirect aspiration on subsequent clearing swallows (28, 36, 37). Patients in our study could not clear post swallow residue, by performing a dry swallow (i.e. a voluntary swallow on request, unstimulated by a bolus) or by swallowing sips of water. Most patients were not aware of pharyngo-oral regurgitation, and we observed no coughing. Pharyngo-oral regurgitation has not yet been described in patients with SMA, but a previous study by Hanayama et al, delineated this phenomenon in children and young adults with Duchenne muscular dystrophy (38). They reported 'difficulty passing the bolus through the cricopharyngeal muscle, combined with some pressure to regurgitate the bolus back into the oral cavity'. We hypothesize that this mechanism is a compensation strategy as a response to bulbar muscle weakness which is described in patients with SMA, (13, 15, 39). It affects the propulsion of the pharyngeal wall, elevation and forward movement of the hyoid, and opening of the cricopharyngeal muscle during swallowing. Pharyngo-oral regurgitation especially occurred in patients who demonstrated abnormal piecemeal deglutition, suggesting that dividing the bolus into small particles, was not a sufficient compensation mechanism.

Muscle ultrasound of bulbar muscles revealed an abnormal muscle structure with a characteristic moth-eaten pattern. Increased echogenicity on muscle ultrasound is caused by replacement of muscle tissue by fatty infiltration in bulbar muscles (14, 33). The moth-eaten pattern consists of dark areas, described as viable motor units as reported by Wijntjes, and areas with increased echogenicity, reflecting permanent denervation and fibrosis (40).

To detect impaired swallowing safety, the questionnaire proved to be helpful. The items 'do you cough when swallowing liquids' and 'do you use antibiotics' corresponded best with unsafe swallowing results of the VFSS (i.e. PAS ≥3). Affirmative replies to both questions are a clear indication for a VFSS. We think that VFSS should be used not only in case of coughing while drinking, but also when patients have difficulty swallowing certain kinds of food, cough while eating solids, or when they have the feeling of food sticking in the throat'. We also advocate the use of clinical swallowing tests and muscle ultrasound in case of reported swallowing problems. It is necessary to prepare

the patient for the possible outcomes of the assessments, for example, the occurrence of aspiration, or that eating solid food is too demanding for the patient and might bring the possibility of pharyngeal residue. Through shared decision making, the professional and patient discuss adaptations with the aim to establish and sustain the feasibility of oral feeding (41).

In this patient group, both swallowing and mastication function were investigated. Mastication problems were characterized by abnormal masticatory efficiency, reduced endurance and fatigue (16). Not surprisingly, mastication problems occurred relatively often - in 60% of the patients - in combination with swallowing problems, and may, therefore, be an indication for a swallowing assessment and vice versa.

Our findings have practical implications for patients. In this study, more than 2/3 of the patients had residue in the valleculae, which is associated with impaired swallowing safety on the subsequent clearing swallow (37). Since we do not know how long pharyngeal residue remains in the hypopharynx after swallowing, nor which method is best for clearing pharyngeal residue, it is recommended not to use coughing techniques (for instance a coughing machine) after mealtime, as these techniques involve deep inhalation and may cause aspiration of residue.

A previous study in patients with SMA (using VFSS and sEMG), revealed more muscle strength when swallowing, and less post swallow residue with the head in a slightly bowed position (15). It is probably best to correct a retracted head position during swallowing, if necessary with a headband, by moving the chin slightly downward and forward, in order to minimize a biomechanical contribution to swallowing difficulties.

In patients with neuromuscular diseases, we should be cautious about thickening liquids because it requires relatively more strength to swallow thick liquids (42). VFSS can be used to determine the correct level of thickness for safe swallowing.

This study has some limitations. A small number of ambulant patients participated in the study. This can be explained by the inclusion criterion of having bulbar problems. Another limitation is that during VFSS, we used for technical reasons a pulse rate of 15 instead of 30 per second. It is possible that we missed milder forms of laryngeal penetration or aspiration. Finally, we did not rate the volume of pharyngeal residue. However, it has been found that BRS was significantly correlated to objective impedance manometry, and that a high BRS score was associated with a higher risk of aspiration (29, 43, 44).

Future research should aim to investigate the results of pharyngo-oral regurgitation in a larger group of patients. Further studies should also involve

the effect of a corrected head position on the amount of post swallow residue. We realize that the current assessment protocol did not capture muscle fatigability related to swallowing. Nearly half of the patients in this study had mealtimes longer than 30 minutes. It is not inconceivable that fatigability negatively affects the performance of swallowing during a meal. Therefore, the relation between muscle fatigability and swallowing is a subject for future research.

Conclusion

In patients with SMA, who report swallowing and/or mastication problems, swallowing problems are characterized by inefficient and sometimes impaired swallowing safety, caused by widespread abnormalities of bulbar muscle structure. Ambulant patients clearly have a better bulbar function compared to non-ambulant patients, but they also show functional and structural abnormalities. These results help to understand the nature of swallowing disturbances in SMA. In this study almost all patients with SMA, who reported problems with eating or drinking, demonstrated disordered swallowing. This is important information for patients who experience swallowing problems, as they can seek help and become properly advised.

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Chapter 5

Feeding and swallowing problems in infants with spinal muscular atrophy type 1: an observational study

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Abstract

Background
Infantile hereditary proximal spinal muscular atrophy (SMA) type 1 is characterized by onset in the first 6 months of life and severe and progressive muscle weakness. Dysphagia is a common complication but has not been studied in detail.

Objective
To study feeding and swallowing problems in infants with SMA type 1, and to explore the relation between these problems and functional motor scores.

Methods
We prospectively included 16 infants with SMA type 1 between September 2016 and October 2018. Eleven infants received palliative care and five infants best supportive care in combination with nusinersen. We compiled and used an observation list with feeding related issues and observed feeding sessions during inpatient and outpatient visits. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was used asa measure of motor function.

Results
All infants in the palliative care group (median onset of disease 14 days (range 1 - 56); median inclusion in the study 52 days (range 16 - 252) demonstrated symptoms of fatigue during feeding and unsafe swallowing. Symptoms were short nursing sessions (10-15 minutes), and not being able to finish the recommended feeding volumes (72%); increased frequency of feeding sessions (55%); coughing when drinking or eating (91%), and wet breathing during and after feeding (64%). Two out of five infants in the nusinersen group (median onset of disease 38 days (range 21 – 90); inclusion in the study at 63 days (range 3 – 218) were clinically pre-symptomatic at the start of treatment. The other 3 infants showed symptoms of fatigue and unsafe swallowing at inclusion in the study. These symptoms initially decreased after the start of the treatment, but (re)appeared in all five infants between the ages of 8 to 12 months, requiring the start tube of feeding. In the same period motor function scores significantly improved (median increase CHOP INTEND 16 points).

Conclusion
Impaired feeding and swallowing remain important complications in infants with SMA type 1 after the start of nusinersen. Improvement of motor function does not imply similar gains in bulbar function.

Introduction

Hereditary proximal spinal Muscular Atrophy (SMA) is a severe autosomal recessive neuromuscular disease caused by survival motor neuron (*SMN*) protein deficiency due to homozygous loss of function of the *SMN1* gene. It is characterized pathologically by atrophy and dysfunction of motor neurons in the anterior horn of the spinal cord and brainstem. SMA has large variation in severity, ranging from infantile (i.e. type 1) to adult (i.e. type 4) onset. The natural history of SMA type 1 is one of rapid decline of motor functions. If left untreated, it is one of the most common genetic causes of infant mortality, due to respiratory failure (1).

Treatment options of children with SMA type 1 have changed dramatically due to technological advances that allow modification of the genetic machinery. Both the antisense oligonucleotide nusinersen and *AAV*-gene therapy have significantly improved survival and motor development of children with SMA type 1 (2-4). Current treatment options are no cure for already clinically symptomatic children with SMA type 1, and the majority will be confronted with limitations later in life. Complementary supportive care as outlined in the revised standards of care therefore remains important (5).

Feeding and swallowing problems are one of the most important complications of SMA type 1 (5-7). Dysphagia in SMA type 1 is described as disturbed and weak sucking, problems with handling oral secretions, weak swallowing with dysfunctional airway protection, and gastroesophageal reflux (GER) (7-10).Dysphagia in SMA type 1 may also lead to other problems such as poor weight gain, discomfort and risk of aspiration pneumonia (9-14). Early and regular monitoring of feeding difficulties at an early stage is recommended in the standards of care (5), but a systematic approach to identify feeding and swallowing problems has not been reported in the literature.

The aim of this study was to describe characteristics of dysphagia in a cohort of infants with SMA type 1 who either received palliative care or best supportive care in combination with nusinersen. The second aim of the study was to explore the relation between functional motor scores and bulbar problems.

Methods

Patients

We prospectively included 16 consecutive patients with SMA type 1, who visited the outpatient clinic of the Netherlands SMA Center at the University Medical Center Utrecht from September 2016 to October 2018. All patients had a homozygous deletion of the survival motor neuron (*SMN*) 1 gene and 2 copies of the *SMN2* gene, as confirmed by using the SALSA multiplex ligation-dependent probe amplification kit P021-B1-01 (MRC Holland, Amsterdam, the Netherlands).

The study protocol was approved by the local medical ethical committee (No. 09-307). Parents of eight infants gave informed consent. Eight other infants (all receiving palliative care) visited the hospital once and then received palliative care at home. We could not obtain informed consent because parents were overwhelmed by emotions after hearing the diagnosis. The clinical data of these infants were used anonymously (in accordance with Article 458 of the Dutch Law of Medical Treatment Agreement).

Treatment with nusinersen versus palliative care

Treatment with nusinersen for infants with SMA type first became available in the Netherlands in May 2017 as part of the expanded access program (EAP) and was reimbursed from August 2018. Parents of children with disease duration of < 26 weeks, and in relatively good clinical condition (i.e. without apparent signs of (impending) respiratory insufficiency) were offered the choice between palliative care and treatment with nusinersen in combination with best supportive care (5). We arranged palliative care if children were in an advanced stage of the disease, i.e. with signs of respiratory insufficiency.

Feeding and swallowing assessment

Two of the authors (AMBH and LVDEH), who are both experienced speech and language therapists specialized in pediatric feeding and swallowing problems in neuromuscular diseases, compiled an observation list based on clinical best practice and the relevant literature (7, 15-23). The presence of feeding abnormalities in all infants was systematically assessed, using the predefined items during inpatient (e.g. for nusinersen treatment) and outpatient visits as part of clinical care.

The items of the observation list covered four main topics:

1. Fatigue related to oral feeding:
   We documented the length and frequency of a nursing session and the presence of sweating when eating or drinking.
2. Unsafe swallowing:
   We documented symptoms of unsafe swallowing (coughing, clearing the throat, and wet breathing) during oral feeding. We observed coughing, due to posterior drooling (i.e. saliva spilled over the tongue into the hypopharynx). We also asked parents if they recognized these symptoms and had noticed them prior to the hospital visit.
3. Regurgitation of food:
   We asked whether infants frequently spit up milk or food or continued to swallow after finishing eating or drinking.
4. Respiratory system:
   We observed the presence of an abdominal breathing pattern and documented respiratory rate, weakness of voice and cough, and frequency of respiratory infections.

Registration of swallowing by videofluoroscopic swallowing study (VFSS)

We performed VFFS in infants from the nusinersen group when we suspected unsafe swallowing. A Philips MultiDiagnost Eleva C-arm was used at a pulse rate of 15 per second. The images were stored in the picture archiving and communication system (PACS). We used an iodine-containing non-ionic radiocontrast agent. We mixed the agent with the milk or pureed food. We visualized the first suck-swallow-breathe sequence, and/or sips of pureed food with the bottle and/or spoon the child was used to. We used the 8-point Penetration-Aspiration Scale, ranging from 1 ('material does not enter the airway') to 8 ('material enters the airway, passes below the vocal folds, and no effort is made to eject') (24).

Motor function assessment (CHOP INTEND score)

Two of the authors (MAGCS and DRW), both experienced pediatric physiotherapists, evaluated the motor function using the CHOP INTEND score at 2, 6 and 10 months after the first gift of nusinersen. This instrument consists of 16 items and assesses the strength during reflexive, spontaneous, or goal-directed movement. The maximum score is 64 points. Lower scores indicate poorer motor function (25, 26).

Relationship between functional motor scores and bulbar problems

We used wet breathing as an outcome measure of unsafe swallowing. To evaluate the effect of nusinersen treatment we used the following categories: 'no wet breathing', 'inconsistent wet breathing' (during feeding), 'consistent wet breathing' (during and after feeding). These scores were compared with the CHOP INTEND values at the start of the treatment, and at 2, 6 and 10 months after the first gift of nusinersen.

Statistical analysis

We used descriptive statistics for patient characteristics, results of the feeding observation list, and CHOP INTEND scores.

Results

Characteristics of patient group

We included 16 out of 19 (84%) consecutive infants with SMA type 1 from May 2016 until October 2018. One child passed away immediately after the diagnosis. Parents of the other two infants could or did not want to participate. Eleven out of 16 (69%) enrolled infants received palliative care and five (31%) received treatment with nusinersen in combination with best supportive care. The parents of three infants (27%) declined treatment and opted for palliative care. Patient characteristics of the palliative care and nusinersen treatment groups are displayed in Table 1. The median onset of disease symptoms, start of tube feeding and CHOP INTEND was higher in the nusinersen group. The age at inclusion and weight did not differ between groups.

Feeding problems in the palliative care group

All infants demonstrated weak sucking. Most infants did not manage to suck with the required vacuum with their tongues, resulting in clicking sounds and/or spilling of milk. The nursing sessions were frequently short, and infants failed to drink the recommended feeding volumes. We observed the following symptoms of unsafe swallowing: 1. coughing; 2. clearing the throat during drinking and 3. wet breathing during and after feeding. Three infants (27%) coughed when drinking, but showed no wet breathing, while seven infants (64%) demonstrated a combination of coughing and wet breathing.

Parents of six infants (55%) reported that they increased the frequency of feedings in order to compensate for feedings that were not finished. Six infants (55%) demonstrated sweating when feeding. Respiratory rate was > 60 per minute in nine infants (82%) (Table 2). Four infants (36%) showed symptoms of regurgitation, as they swallowed frequently after tube feeding. All infants had an abdominal breathing pattern. Their cough and cry were weak. Three infants (27%) had respiratory infections. All infants started tube feeding directly or within a few days after visiting the hospital.

Table 1. Patient characteristics

	Palliative care group (n=11)	**Nusinersen group (n=5)**
Male : Female	8 : 3	3 : 2
2 SMN2 copies	10 *	5
Age at inclusion (days)	52 (16 – 252)	63 (3 – 218)
Weight at inclusion (SD)**	0,78 (-2,6 – 2,1)	0,73 (-0,5 – 1,3)
Onset of disease symptoms (days)	14 (1 – 56)	38 (21 – 90)***
Start of tube feeding (days)	52 (19 – 252)	382 (63 – 445)
CHOP INTEND at inclusion	19 (4 – 35)	34 (17 – 46)
pCO_2 > 45 mmHg	4****	1

Data are n or median (range). *SMN2:* survival of motor neuron 2. *Not available from 1 patient. **Growth curves based on the fifth national growth study in the Netherlands (www.tno.nl/groei). SD: standard deviation.***Infant 7 was prenatally diagnosed. CHOP INTEND: Children's Hospital of Philadelphia Infant Test for Neuromuscular Diseases.**** Not available from 4 patients.

Table 2. Feeding characteristics of infants with SMA type 1 in the palliative care group, at inclusion in the study.

Infant	CHOP INTEND score	Short nursing sessions, without finishing feeding	Increased frequency of nursing sessions	Coughing when feeding	Wet breathing during or after feeding	Clearing throat when feeding	Sweating when feeding	Respiratory rate (per minute)
1	18/64	-	-	-	-	-	+	60
2	14/64	-	-	+	+	-	-	55-72
3	21/64	+	-	+	+	-	-	60-70
4	4/64	-	-	+	+	-	-	>60
5	24/64	+	+	+	-	-	+	80
11	19/64	+	+	+	+	-	+	35
12	20/64	+	+	+	+	-	+	<40
13	35/64	+	+	+	+	-	+	60
14	18/64	+	+	+	-	-	-	60
15	14/64	+	+	+	-	+	-	50-80
16	21/64	+	-	+	+	+	+	>60
		72%*	**55%**	**91%**	**64%**	**18%**	**55%**	

* Percentage of 'yes'. - = No, + = Yes

Table 3. Feeding characteristics of infants with SMA type 1 in the treatment group, at inclusion in the study.

Infant	CHOP INTEND at inclusion in the study	Short nursing sessions without finishing feeding	Frequent nursing sessions	Coughing when feeding	Wet breathing during or after feeding	Clearing throat when feeding	Sweating when feeding	Respiratory rate (per minute)
6	17/64	+	+	-	+	-	+	40-50
7	43/64	-	-	-	-	-	-	44
8	34/64	+	+	+	+	-	+	<40
9	46/64	-	-	-	-	-	-	42
10	20/64	-	-	+	+	-	+	40-60
		40%*	**40%**	**40%**	**60%**	**0**	**60%**	

* Percentage of 'yes'. - = No, + = Yes

Feeding problems in the nusinersen group

Two infants (7 and 9) who were clinically pre-symptomatic at enrollment did not show symptoms of feeding problems (Table 3). The parents of both infants had previously lost children with SMA type 1 (the sibling of infant 7 died at the age of 2 months, the sibling of infant 9, at the age of 7 months). Nusinersen was started seven days (infant 7) and 56 days (infant 9) after birth respectively. The other three clinically symptomatic infants had a weak suck and cough and showed wet breathing when eating or drinking. After the start of treatment with nusinersen, sucking and swallowing improved. For example, infant 10 was able to breast-feed for a few minutes without symptoms of unsafe swallowing. She also received partial tube feeding. Two months after the start of treatment, breast feeding sessions had normalized (i.e. without coughing or wet breathing).

This initial improvement of bulbar function was temporary in all five treated infants. Between the ages of 8 to 12 months respiratory infections and coughing or wet breathing reappeared. VFSS showed silent aspiration in four out of five (80%) infants. The first VFSS examination of the fifth infant (infant 8) at the age of 8 months was not successful. At the age of 21 months a second VFSS demonstrated laryngeal penetration. All infants treated with nusinersen eventually needed tube feeding (median start at 382 days (range 63 – 445).

Relationship between functional motor scores and bulbar problems

The median CHOP INTEND score at baseline was 19 (range 4 – 35) in the palliative group, and 34 (range 17 – 46) in the nusinersen group. The infants with CHOP-INTEND scores in the range of 4-35 points all coughed or showed wet breathing during or after drinking. The feeding observations of the two clinically pre-symptomatic infants with CHOP INTEND scores of 43 and 46 at inclusion in the study, showed no symptoms of fatigue or unsafe swallowing.

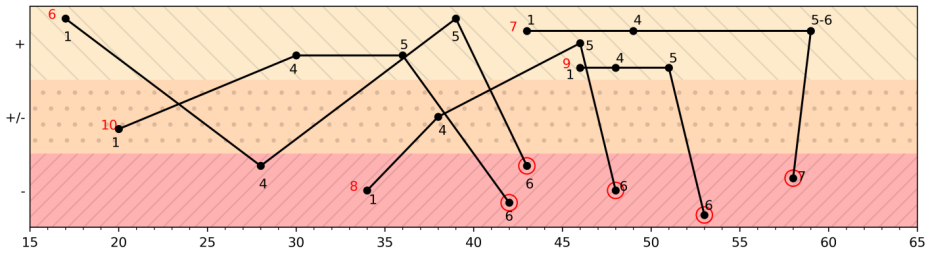

Figure 1. The CHOP INTEND scores (x-axis) in relation to bulbar function (y-axis), during the course of treatment with nusinersen (gift 1,4,5,6) of infant 6 – 10

+ = No wet breathing, +/- = Inconsistent wet breathing, - = Consistent wet breathing, ○ = Timepoint of VFSS

After 6 nusinersen gifts the median CHOP INTEND was 48 (range 42-59 points). In this first year of treatment, the median increase in the CHOP INTEND score was 16 points (range 7-26). Despite this improvement, all five treated infants showed a deteriorating swallowing function between the ages of 8 to 12 months (Figure 1). Unsafe swallowing was confirmed with VFSS.

Discussion and conclusion

In this study we systematically assessed feeding of infants with SMA type 1. As expected, all clinically symptomatic infants showed varying symptoms of insufficient drinking and fatigue during feeding, which eventually resulted in unsafe swallowing. These symptoms appeared gradually, and parents could not specify when problems started. Treatment with nusinersen improved swallowing quality in the first half year of life but deteriorated in all, including 2 infants in whom treatment had been started when they were clinically pre-symptomatic. The gains in motor function as shown by increasing CHOP INTEND scores were not matched by improvement of bulbar function. After initial improvement of the swallowing and feeding abnormalities, the swallowing function deteriorated between the ages of 8 to 12 months. Symptoms and severity of dysphagia in the nusinersen group were comparable to the palliative care group. Our data suggest that continuous monitoring of feeding problems in treated infants with SMA type 1 is important.

SMA affects motor neurons in the spinal cord and the brainstem (27) and abnormal bulbar function is a well-known complication of SMA type 1 and 2 (7-10, 28). Feeding is an important topic in the standards of care (5) but there are few studies that have systematically addressed the nature and prevalence of abnormalities in infants with SMA type 1. We observed feeding abnormalities in all infants, although symptoms varied. The most frequent abnormalities were coughing and shortened nursing sessions. This latter symptom easily goes unnoticed, as parents often increase the frequency of feeding with the aim of achieving sufficient intake and probably not always inform caregivers of these adaptations. Choking was easily overlooked because all infants demonstrated weak, ineffective coughing. We also found that 'wet breathing' occurred after a period of (soft) coughing when drinking and that in these cases VFSS showed, without exception, silent aspiration or silent laryngeal penetration. In addition, many children showed signs of fatigue, including sweating and an increased respiratory rate. High respiratory rate further complicated the coordination of swallowing and breathing when drinking, which may be associated with

feelings of distress and aspiration (22, 23). Limited endurance of muscle activities is a feature of SMA (29) that probably also affects bulbar muscles during swallowing and chewing. Our findings indicate that signs of relevant feeding abnormalities may be subtle and that feeding observations should be performed systematically and at short intervals.

This is to the best of our knowledge the first study that has systematically investigated the impact of nusinersen on bulbar functions. Recent findings suggest that nusinersen upon intrathecal administration disseminates throughout the central nervous system (30), but that delivery to motor neurons in the brainstem may be less efficient than to the lumbar and thoracic segments of the spinal cord (31). Our data suggest that this has functional consequences, since even children in whom we started treatment with nusinersen before the onset of muscle weakness, demonstrated symptoms of abnormal feeding before their first birthday.

Feeding abnormalities may not only be seen in infants treated with intrathecally administered nusinersen. Data from the phase 1 trial with AAV9-*SMN1* gene therapy that has been approved for market access in the United States, suggest that not all treated infants could do without tube feeding, after a follow up of more than 20 months (2). This suggests the possibility that brainstem motor neurons are relatively vulnerable despite genetic treatment. We think that future studies should therefore include frequent and systematic assessments of feeding and bulbar functions of clinically symptomatic and pre-symptomatic children to monitor the long-term results of all genetic therapies.

It is important to note that motor function scores, which are used to evaluate response to treatment, do not necessarily completely correlate with bulbar function and do not predict the absence of bulbar dysfunction.

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Chapter 6

General discussion

Dysphagia may have a major impact on the lives of patients with neuromuscular diseases (NMDs). The characteristics and underlying disturbed mechanisms, causing dysphagia in proximal spinal muscular atrophy (SMA; 5qSMA) have not been elucidated. This thesis aims to contribute to a better understanding of the bulbar problems, and its consequences.

SMA is one of the more common hereditary neuromuscular diseases with onset in infancy or childhood. Over the past years, there have been major developments in the pharmacological treatment of SMA. Since the introduction of treatment with nusinersen (Spinraza®), risdiplam (Evrysdi®) and Onasemnogene abeparvovec (zolgensma®), life expectancy and quality of life of patients with SMA has changed tremendously. In the large majority of children treated with nusinersen, motor function improved, or stabilized (1).

During the period of study covered by this thesis, the first infants with SMA were treated with nusinersen. We described the effects of nusinersen on the bulbar function in symptomatic infants (Chapter 5). In the other studies of this thesis, we included patients who did not yet have access to these therapies (Chapters 2, 3, 4). This meant we were able to describe the swallowing function of treatment naïve patients with SMA, who reported bulbar problems (Chapters 3, 4).

Table 1a and 1b. Comparison of the studies of Chen et al., Messina et al. and van der Heul et al. (Chapter 2) (3, 4).

	Chen et al.	**Messina et al.**	**van der Heul et al.**
Number of patients	108	122	112
SMA type	SMA type 2 + 3	SMA type 2	SMA type 1-4
Analysis per SMA type	Analysis of SMA type 2+3 combined	N.A.	Analysis per SMA type
Age range in years	1 – 45 (not subdivided)	1 – 47 (subdivided into 6 groups)	1 – 75 (subdivided into 6 groups)
Number of patients with non-invasive or invasive ventilation	11/108	19/122	7/11 (SMA type 1) 14/55 (SMA type2) 3/26 (SMA type 3a) 0/26 (SMA type 3b/4)
Body weight recorded	yes	yes	no
Active maximum mouth opening (in mm)	Yes	Yes	Yes
Motor function	Classified as walker, sitter, non-sitter	Classified as sitter	HFMSE

This chapter presents a discussion of the self-reported bulbar problems in children and adults with SMA (Chapter 2), as well as the characteristics and underlying disturbed mechanisms of dysphagia in adolescent and adult patients with SMA (Chapters 3, 4). Finally, we will address dysphagia in infants with SMA type 1 (Chapter 5). The insights obtained, provide the basis for recommendations and improvement of the quality of care for SMA (Chapter 6).

Table 1b.

	Chen et al.	**Messina et al.**	**van der Heul et al.**
Method	Semi-structured Interview live	Semi-structured Interview by phone	Self-administered written questionnaire
Type of questions	Binary	Binary	Binary
Questions about jaw opening	Yes	Yes	Yes
Questions about mastication difficulties	Yes	Yes	Yes
Questions about swallowing	Choking (solid/ semi-solid/liquid) Dysphagia (solid/ semi-solid/liquid) 'Sensation of food sticking in chest/ throat or regurgitaton, or repeated attempts to swallow'	Choking (liquid/ semi-solid/solid/ both liquid and solid) Aspiration Swallowing difficulties Repeated swallowing	Choking Coughing with liquids Coughing with solids Difficulty swallowing (solid, puree/thick liquid/liquid/both solid and liquid) Feeling of food getting stuck in throat (solid, puree/thick liquid/liquid/both solid and liquid)
Questions about diet modification	Dietary modification*	Dietary modifications such as changes in the consistency or quantity of food administered	Dietary modifications by cutting into small pieces, pureeing or avoiding hard foods (such as apple or baguette)
Questions about mealtime duration	Yes (mealtime duration > 30 minutes)	Yes (mealtime duration in minutes)	Yes (mealtime duration > 30 minutes)

*Results not reported

Patient characteristics of the studies in Table 1a and 1b, active maximum mouth opening and motor function. HFMSE: Expanded version of the Hammersmith Functional Motor Scale, which combines the original HMFS with an add-on module, and can distinguish motor skills among individuals with SMA 2 and 3. Presentation of method of the studies, content of the questionnaires.

6.1. Aim ① To provide insights into self-reported bulbar problems across the full age and severity spectrum of SMA and the relationship with age, motor function and active maximum mouth opening.

The study in Chapter 2 investigated reported jaw, mastication and swallowing problems. We used the DDD(p)NMD, a questionnaire used by Dutch speech language therapists (SLTs) working with patients with NMDs (2) (see appendix). Although there is an overlap between the present work and studies by Chen et al. and Messina et al.(3, 4), there is a difference: we included patients over the entire severity spectrum of SMA, and we included patients over 50 years of age (Table 1).

An important finding of our study was that 56% of the patients reported choking. In the studies by Chen et al. and Messina et al., the frequency of choking was 25-33% (3, 4). This can be explained by the fact that we included both patients with the most severe phenotype of the spectrum (i.e. SMA type 1c) and older patients. In addition, the study in Chapter 2 included relatively more patients with (non-)invasive ventilation, which is associated with more feeding difficulties (3, 4).

A new finding in Chapter 2 is that relatively few patients reported coughing when eating or drinking. Coughing is a normal response on a blockage of food in the hypopharynx, or on liquids entering the airway. A possible explanation could be the unexpected observation of pharyngo-oral regurgitation during the swallowing study (Chapter 4). Patients who did not manage to swallow the bolus in one swallowing action, transported the bolus back to the oral cavity without coughing. This process would not go unnoticed by the patient and might be reported as a choking episode.

In addition to detecting mastication and swallowing problems, the questionnaire may also illuminate the extent of a problem, by combining the results of specific questions. As an example, we compared the results of reported mastication difficulties, diet modification and mealtime duration. Patients who reported no problems with mastication probably had mild mastication problems when they simultaneously reported diet modification. The dietary modification may have ensured normal mealtime duration. Patients who reported mastication problems and diet modification, but normal mealtime duration probably had moderate mastication problems. The patients with mastication difficulties, diet modification and prolonged mealtime duration probably had severe mastication problems.

There has been no psychometric evaluation of the questionnaire, but some properties referring to validity and reliability can be mentioned. The questionnaire consists of questions that substantively overlap the

questionnaires of Messina and Chen (3, 4). These questions have also been used in studies of swallowing problems in DMD (5). This suggests face validity of the DDD(p)NMD. Evidence supporting construct validation was the decreasing frequency of reported bulbar problems in the less severe forms of SMA. Lastly, we showed that intra-reliability was established in a small group of patients (Chapter 2).

6.2. Aim ② To describe characteristics, symptoms and the underlying mechanisms of mastication and swallowing problems, in adolescents and adults with SMA types 2 and 3 (Chapter 3 and 4).

The questionnaire findings led to the design of a clinical study of the precise problems experienced during mastication and swallowing (Chapters 3, 4). We only enrolled patients with reported mastication and/or swallowing problems, as the ethical committee considered that participation of patients without reported problems would be an unacceptable burden.

The clinical and instrumental mastication and swallowing assessments are presented in Figure 1.

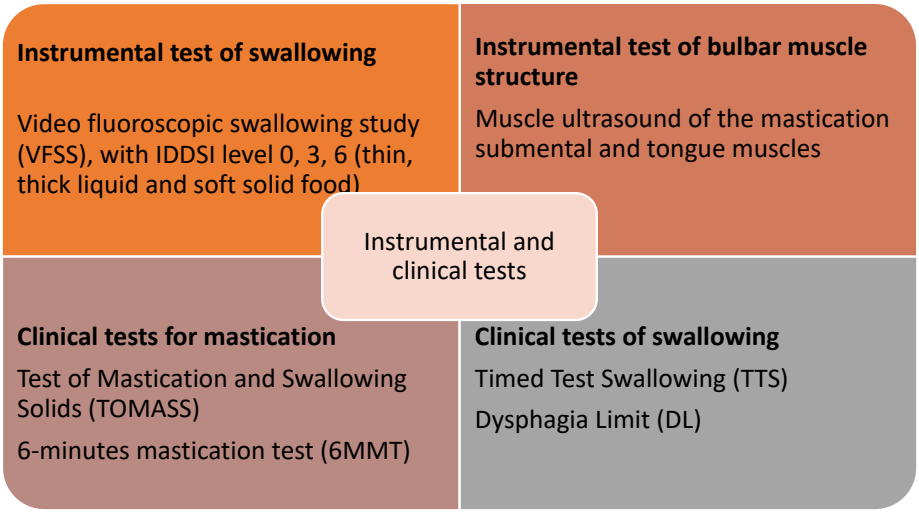

Figure 1. Overview of the instrumental and clinical tests applied.

The combination of instrumental and clinical tests made it possible to compare the results of both a real time view of the swallowing action with a video fluoroscopic swallowing study (VFSS), ultrasound images of the muscle

structure, and the functional performance of mastication and swallowing of the patient (i.e. the clinical tests of swallowing and mastication).

VFSS enables the assessment of efficiency and safety of swallowing. The disadvantage of VFSS is radiation exposure. Also, the patient needs to swallow a combination of food and contrast material, instead of only actual food. It is also possible to visualize the pharyngeal phase of swallowing by applying flexible endoscopic evaluation of swallowing (FEES), but, understandably, patients often consider inserting the scope through the nose as invasive. In our study, we analyzed the VFSS semi-quantitatively, using the penetration-aspiration scale and the bolus residue scale, as this provides the most important functional information about swallowing performance (6, 7). We used qualitative muscle ultrasound, as applied in the paper of Lagarde et al. for example, to investigate changes in the bulbar muscle structure (8). Magnetic resonance imaging studies of bulbar muscles have been performed previously, but ultrasound offers the advantage of being quick to perform and without radiation, as well as being able to assess structural changes of multiple clinically relevant muscle groups including the tongue (9, 10). The clinical mastication and swallowing tests used in this study, are validated tests (11-16).

We found evidence that muscles weakness and reduced endurance (i.e. fatigability) underlie inefficient mastication and swallowing. The characteristics, symptoms and underlying disturbed mechanisms of mastication and swallowing problems in SMA are presented in Figure 2.

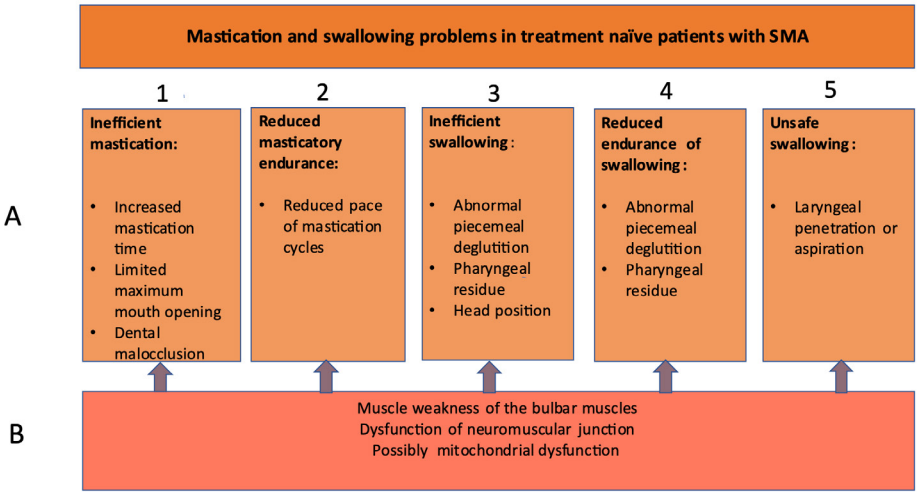

Figure 2. Overview of characteristics (A) and underlying disturbed mechanisms (B) of mastication and swallowing problems in patients with SMA.

We will elaborate on the details of the five characteristics, and explain the disturbed underlying mechanisms presented in Figure 2.

Characteristic 1. Inefficient mastication

Increased time of mastication

In patients with SMA, increased time required to eat a standard cracker is caused by muscle weakness of the mastication muscles. On muscle ultrasound the mastication muscles (i.e. masseter, and temporalis muscles) and tongue muscles showed an increased echogenicity, which is associated with muscle weakness and atrophy (17) (Chapter 3).

Muscle weakness is primarily caused by the loss of motor neurons in the anterior horn of the spinal cord, medulla oblongata and pons (18). Although motor neurons are the tissue most sensitive to the deficiency of intracellular *SMN* protein, muscle tissue may also require sufficient levels of *SMN* protein to function properly. Hence, there may be secondary mechanisms that contribute to muscle weakness in addition to denervation (19). Quantitative Magnetic Resonance Imaging (MRI) studies have shown fatty degeneration of skeletal muscle groups over the course of one year (20). An MRI study of bulbar muscle groups in 12 patients with SMA types 2-4 showed similar abnormalities with mildly affected mastication muscles (i.e. mild fatty infiltration and/or atrophy of the muscle), moderately affected submental muscles (i.e. digastric muscles, and geniohyoid muscles) and a severely affected lateral pterygoid muscle in non-ambulant patients (9).

There are two more complications leading to inefficient mastication in patients with SMA. These are limited active maximum mouth opening (aMMO) and dental malocclusion.

Limited aMMO

Limited aMMO is a common symptom in patients with SMA, caused by structural changes of the lateral pterygoid muscle (9). The results of the study in Chapter 3 confirmed limited aMMO (i.e. < 40 mm) in 88% of the patients with SMA type 2, and in 44% of the patients with SMA type 3. Ambulant patients had a normal aMMO. Importantly, limited aMMO correlated significantly with inefficient mastication (Chapter 3). This is explained by a limitation in both vertical and horizontal jaw movements, that are essential for grinding the food efficiently (21).

Consequences of limited aMMO include insufficient dental hygiene, problems with dental care, or problems with endotracheal intubation (22). Inadequate oral hygiene may facilitate pathogenetic bacteria, associated with pneumonia (23).

Efficacy of interventions to increase aMMO has not been investigated in detail. Only two studies described a jaw stretching program using a Therabite device, in a total of four SMA patients (24, 25). The results showed that patients (23-62 years of age) preserved or slightly increased (5-7mm) aMMO. Patients were adults, and already had limited aMMO at the start of the training program (i.e. 15 – 21 mm) (24, 25). Future studies need to investigate efficacy of jaw stretching programs.

Dental malocclusion

The study in Chapter 3 revealed that two third of the patients with SMA type 2 and 3 had dental malocclusion (Chapter 3). This means that the number of occluding teeth necessary to grind food efficiently, is reduced (26). Another consequence of malocclusion is an altered mastication pattern. According to Piancino et al., the central pattern generator in the brainstem lacks sensory information due to elements of the teeth that do not touch each other during mastication. As a result, the masticatory movements and the duration of the chewing cycle (opening and closing of the jaw) become smaller as reflected by shorter closing times of the jaw and a lower sEMG amplitude of the temporal and masseter muscles (27). In our study, the majority of the non-ambulant patients did indeed have small jaw movements during mastication, although this could also be explained by limited aMMO (Chapter 3).

Dental malocclusion in SMA (i.e. the abnormal position of teeth in the same and/or opposite jaw, when the jaws are closed), is caused by facial muscle weakness, resulting in a relatively large vertical development, particularly in the lower part of the face. Houston et al. described a prevalence of malocclusion in 60% of the children with SMA (28, 29).

Characteristic 2. Reduced masticatory endurance and perceived fatigue

Patients demonstrated a slow pace of mastication or dropped out (failing to complete the test) of the 6-minutes mastication test (Chapter 3). This reduced endurance of repeated motor tasks is common in patients with SMA and is also known as fatigability (30).

Fatigability in patients with SMA has recently been extensively studied in patients with SMA types 2-4, using a series of shuttle tests using the same construct, i.e. performing a series of repetitive tasks (place and return pegs in holes, move blocks over a partition or walk a distance repeatedly) at a constant pace of 75% of the individual's maximal capacity (30-36). Patients with fatigability were unable to continue such a repetitive motor function task at a submaximal exercise intensity. This abnormal endurance has been demonstrated in 85% of the patients with SMA but is not seen in patients with other neuromuscular diseases and comparable motor function levels. Moreover, fewer patients with other neuromuscular diseases and comparable motor function levels dropped out. Therefore, just like muscle weakness, fatigability is thought to be an important and specific feature of SMA. (32, 33, 35). Bartels et al. found that fatigability was significantly associated with muscle strength and motor function, but it was also observed in patients with a preserved motor function (31, 32). The prevalence of masticatory fatigability in Chapter 3 was lower than in the skeletal muscle study of Bartels. A possible explanation may be that the 6-minute mastication test is less sensitive in detecting fatigability since it does not use a predefined pace of chewing. Another explanation may be that masticatory muscles, like respiratory muscles, are less sensitive to fatigability (37).

Importantly, fatigue levels (i.e. perceived fatigue) reported by patients were not associated with fatigability (32). The study results in Chapter 3 are in line with these observations; patients with and those without fatigability during mastication reported increased fatigue. We also found that perceived fatigue was significantly increased compared to healthy subjects, both in non-ambulant and ambulant patients (12).

The underlying mechanism of fatigability is probably multifactorial. These factors include the loss of motor neurons, dysfunction of the neuromuscular junction, and possibly mitochondrial dysfunction (33, 34, 38). Specific evidence for dysfunction of the neuromuscular junction has been shown in half of the patients with SMA types 2 and 3, using relatively insensitive EMG techniques (38). Acetylcholine inhibitors facilitate neuromuscular transmission, and a placebo-controlled phase 2 study with pyridostigmine showed an improvement of patient reported fatigability and a decreased risk of drop-out (70%) during the shuttle test (39).

The effect of pyridostigmine on mastication has, as not yet been investigated, although adult patients with problems finishing their meals reported beneficial effects. This may be the subject of future study, using

a shuttle mastication test (i.e. with a predefined pace of chewing) or alternatively the TOMASS, before and after starting medication.

Characteristic 3. Inefficient swallowing

The study in Chapter 4, showed that swallowing problems in patients with SMA, are more pronounced for solid food than for liquids. Sixty seven percent of the patients reported difficulties swallowing solid foods, compared to 11% who reported problems with liquids. A previous study by van den Engel-Hoek et al., described that more muscle strength and time was needed to swallow solid or thick liquid food, compared to thin liquid (40). It is, therefore, likely that when muscles progressively weaken, the first swallowing problems will occur with solid food. The first complaint reported by less severely affected (for instance ambulant) patients was indeed the feeling of solid food getting stuck in the throat.

Other common features of inefficient swallowing are abnormal piecemeal deglutition and pharyngeal residue.

Abnormal piecemeal deglutition

Abnormal piecemeal deglutition is characterized by swallowing a bolus volume of a normal size in 2 or more swallows. We observed abnormal piecemeal deglutition in 79% of the non-ambulant patients (Chapter 4). Muscle weakness of the tongue, submental and pharyngeal muscles may contribute to abnormal piecemeal deglutition. In addition, it is not inconceivable that a retracted head position due to weak neck muscles in patients with SMA may lead to changes in the anatomical space of the pharynx (16, 41, 42) (Figure 3).

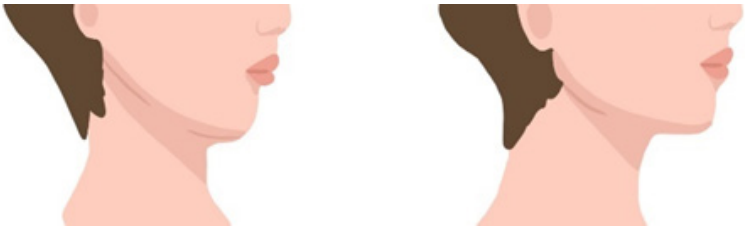

Figure 3. retracted and neutral head position

A previous study by van den Engel-Hoek et al. showed that with the head in a forward position (i.e. slightly bowing the head forward), successful swallowing

could be achieved with less muscle strength. In addition, this was accompanied by a larger swallowing volume, and less pharyngeal residue (43, 44). These observations should be used by health professionals to improve the quality of swallowing.

Pharyngeal residue and pharyngo-oral regurgitation

Pharyngeal residue, which occurred with thin liquid, thick liquids and solid food in 79%, 88% and 22% of the patients, could not be removed by the patient shortly after swallowing, by re-swallowing, or by taking a sip of water (Chapter 4). The study protocol unfortunately did not allow the time needed to clear residue from the hypopharynx to be determined because this requires fluoroscopy.

We unexpectedly observed a phenomenon of pharyngo-oral regurgitation (Chapter 4). Hanayama et al. previously reported pharyngo-oral regurgitation in patients with Duchenne muscular dystrophy (DMD) (45). In patients with SMA, the bolus often remained in the hypopharynx for more than a second, before it was transported back to the oral cavity. The patient was apparently able to adapt and tolerate the bolus in the sensitive hypopharynx, without symptoms of stress, or coughing. This is striking, as sensory loss is not part of the disease (18, 46).

Pharyngeal residue is caused by incomplete pharyngeal constriction, which is suggestive for pharyngeal muscle weakness and reduced tongue base pressure (47, 48). Residue is considered to form a risk of aspiration on the subsequent swallow (i.e. indirect aspiration)(49, 50). This was indeed observed in some patients during VFSS (Chapter 4).

Characteristic 4. Reduced endurance of swallowing

Abnormal piecemeal deglutition and pharyngeal residue

In the study in Chapter 4 we did not address the possibility that swallowing is complicated by reduced endurance (fatigability). Fatigability during swallowing may lead to the same features as described above when explaining inefficient swallowing (characteristic 3), specifically pharyngeal residue and/or abnormal piecemeal deglutition. Warnecke et al., described fatigability of swallowing in patients with myasthenia gravis, the prototypic disorder of neuromuscular junction dysfunction. When swallowing pieces of bread, an increase in pharyngeal residue appeared as the number of swallows increased (51). Another study showed that fatiguing exercises of the tongue caused a decreased anterior

and posterior maximal tongue pressure during swallowing in healthy adults (52). The posterior part of the tongue plays an important role in the propulsion of the bolus through the pharynx during swallowing (see under characteristic 3) (16, 41, 42). These results imply that fatigability of swallowing may be present in swallowing in patients with SMA, as we observed both abnormal piecemeal deglutition and pharyngeal residue (Chapter 4). Future research should clarify if fatigability during swallowing is present in patients with SMA. Finding sensitive outcome measures for fatigability in swallowing is however challenging, but kinematic and temporal outcome measures, using VFSS, could be inventoried. Also, manometry of the pharyngeal muscles could be considered.

Characteristic 5. Unsafe swallowing

Laryngeal penetration or aspiration

Muscle weakness causes a reduced upward and forward movement of the hyoid, and laryngeal elevation, and may result in an insufficient protection of the airway by the epiglottis during swallowing (53, 54). An important novel finding in the study described in Chapter 4, was that five of six patients with laryngeal penetration or aspiration (penetration-aspiration scale Rosenbek > 3), did not try to clear the airway. In other words, these patients did not notice that they were choking. All patients except one reported coughing when swallowing liquids. It is therefore good to also pay attention to reported respiratory infections in combinations with daily use of antibiotics because these characteristics can also indicate unsafe swallowing. In addition, the SLT can observe a patient when drinking sips of water, using laryngeal auscultation. Wet breathing after swallowing is a symptom of laryngeal penetration or aspiration.

Relation self-reported problems with clinical and instrumental tests

We used the questionnaire DDD(p)NMD In combination with the instrumental and clinical assessments (Chapters 3, 4). Comparing the patient reported problems with the results of the clinical and instrumental tests allowed us to check whether there was underreporting of mastication and/or swallowing problems. Underreporting of dysphagia has previously been described in neurological diseases, and more specifically neuromuscular diseases (45, 55-58). In the study in Chapter 3, underreporting of mastication problems occurred in approximately one of four patients. This was also noted by van Bruggen et al.,

who described that patients did not complaint about mastication, but applied diet modification (59). This indicates that patients get used to, and adapt to the masticatory deterioration during disease progression. In our study, swallowing problems did not seem to be underreported, except for one patient who demonstrated silent aspiration (i.e. aspiration without coughing), which we discussed previously. Swallowing problems in SMA are often accompanied by the feeling of food getting stuck in the throat, which can lead to choking. The unpleasant feeling of a blockage of food is possibly the reason that there is less underreporting of swallowing problems, than of mastication problems.

The underlying mechanism of mastication and swallowing problems

We found evidence that bulbar muscle weakness is an underlying mechanism of mastication and swallowing problems in SMA. Ultrasound of the bulbar muscles, increased echogenicity was accompanied by a moth-eaten pattern in many patients with SMA (Chapters 3, 4). The ultrasound appearance of this non-homogeneous increased echogenicity of the bulbar muscles, differentiates SMA from other muscle diseases, such as DMD and Myotonic Dystrophy (MD) (60-62). We qualitatively analyzed the images to investigate changes in the muscle structure of patients with SMA types 2 and 3. The use of a quantitative analysis is more objective and allows one to detect changes in muscle structure, for instance to track disease progression. In patients with SMA, quantitative analysis of muscle ultrasound is complicated by the fact that the inhomogeneous ultrasound appearance of muscles of patients with SMA results in a less increased z-score of echogenicity, despite the visually clearly abnormal images (63). In muscle diseases such as DMD and OPMD, quantitative muscle ultrasound has been successfully applied to demonstrate disease progression (53, 64).

MR imaging of bulbar and skeletal muscle is both qualitatively and quantitatively abnormal in patients with SMA and is sufficiently sensitive to detect changes in the course of one year (9, 20, 65). The clear advantage of muscle ultrasound is the possibility that it can be used from the earliest age without sedation; it would, therefore, be valuable to explore other analytical methods for quantification.

Conclusion aim ②

The studies in Chapter 3 and 4 demonstrate that muscle weakness and reduced endurance cause complex mastication and swallowing problems in treatment naïve adolescents and adults.

The care for adolescents and adult patients with SMA and mastication and/or swallowing problems

International standards of care have been developed to provide a benchmark of good health care for patients with SMA. However, these statements do not provide detailed information about of the content of care and have been developed for the needs of children (66). Recently, two studies from the USA and UK described that adult patients with neuromuscular disorders must do without the multidisciplinary approach as presented in the standards of care for children. As a result, specific care questions of patients remain unanswered (67, 68). This indicates that there is a need for (multidisciplinary) standards of care for adults. The care for mastication and swallowing problems is a clear example.

In the Netherlands, adult patients may well visit a rehabilitation physician or neurologist regularly, but it seems they rarely ask for help for mastication and swallowing problems. This is an unmet need, given the severe swallowing problems we observed in non-ambulant patients (Chapters 3, 4) and the high percentage of swallowing problems reported by adults (Chapter 2). It is important that standards of care are developed and amended to ensure better guidance for these patients. For adolescents, standards of care should incorporate the transition to adult care. The standards of care for adults should include an annual search for the red flags of unsafe swallowing: coughing with solid foods and/or liquids. Coughing with solid foods is most likely a reflection of a food blockage in the hypopharynx. Coughing with liquids reflects liquid going into the airway. Both situations are precarious for the patient; they can lead to asphyxia or can cause lung infections.

Standards of care should also include the use of the DDD(p)NMD to detect milder problems than unsafe swallowing that are a reason for further investigation, such as difficulty with mastication, difficulty swallowing certain kinds of food, and jaw cramps during mastication.

When the patient is referred to the SLT, we advocate the use of quantitative mastication and swallowing tests (11-16). These tests not only help determine the diagnosis, but also allow the monitoring of disease progression, or effect of treatment. To monitor disease progression, a biennial check with clinical tests may be appropriate, given the relatively slow decline in swallowing function. In the following year, there could be a video consultation with an interview, to check whether there have been any changes in symptoms. If this is the case, the patient can come to the hospital for a consultation with the SLT.

In Europe and the USA, SLTs are predominantly involved in the care for mastication and swallowing problems. In some countries, for instance the United Kingdom, there is a shortage of professionals specialized in

dysphagia. Only a small proportion of patients with SMA has access to an SLT (68). The result is that other allied health professionals, such as occupational therapists, or physiotherapists may be involved to observe the bulbar function. They may not have the expertise to perform quantitative assessments of the bulbar function (69). If only a questionnaire is used, there is a risk of missing mastication problems or unsafe swallowing.

Recommendations care for adolescents and adults with SMA

Most patients with SMA consider eating and drinking to be an important activity and they want to sustain oral feeding for as long as possible. The SLT will, therefore, do everything to explore all options for oral feeding (70, 71). After the assessment, the rehabilitation goals are determined in collaboration with the patient. In achieving these goals, the SLT can use the following recommendations intended to support mastication and swallowing. General conditions for safe eating and drinking will be discussed first.

General conditions related to eating and drinking

Body posture and head position are central to safe swallowing. The optimal posture for eating and drinking for non-ambulant patients, is sitting in an adapted wheelchair, with a stable and as symmetrical posture as possible and an optimal head position (44, 72, 73). Measures to maintain an optimal head position during mealtime can be taken in consultation with the occupational therapist. An option is to use a head band, or a headmaster collar. Other safe feeding postures may be supported upright sitting in bed, or in a side lying position, provided that a neutral head position is adopted (74). For successful eating and drinking, a patient should be well rested. If the patient must eat when in a tired state, it is recommended that the consistency of the food should be (thick) liquid.

Figure 4 summarizes recommendations related to head position during eating and drinking.

Optimize efficient mastication

To preserve the condition of the mastication muscles, we suggest chewable foods are eaten every day (Figure 5). At the same time, it is important to maintain a mealtime duration comparable to family/friends, to avoid fatigue in neck muscles (responsible for keeping the head in an optimal position). Part of the solid food can then be replaced by diet foods, or a blended soup (for instance using the ingredients of the meal).

Inefficient mastication may be caused by limited aMMO. This contracture of the jaw hinders the movement of the jaw vertically and horizontally necessary to grind the food thoroughly. To preserve aMMO as much as possible, we recommend jaw stretching exercises, although efficacy of jaw stretching has not yet been comprehensively studied (24, 25). Eventually, in some patients, aMMO may further decrease in less than 15 mm (22). The aim of jaw exercises is to slow down the decreasing aMMO, or to maintain the current aMMO.

In the treatment of limited aMMO, SLTs can stretch the jaw by placing an incremental number of spatulas horizontal between the jaws and in the same direction as the lips, until there is a sensation of painless stretching (Figure 6).

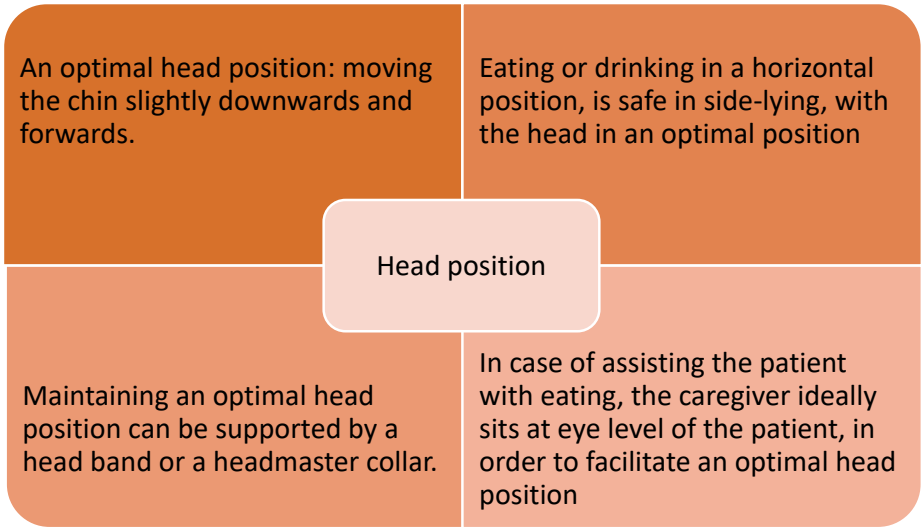

Figure 4. Recommendations for head position during eating and drinking.

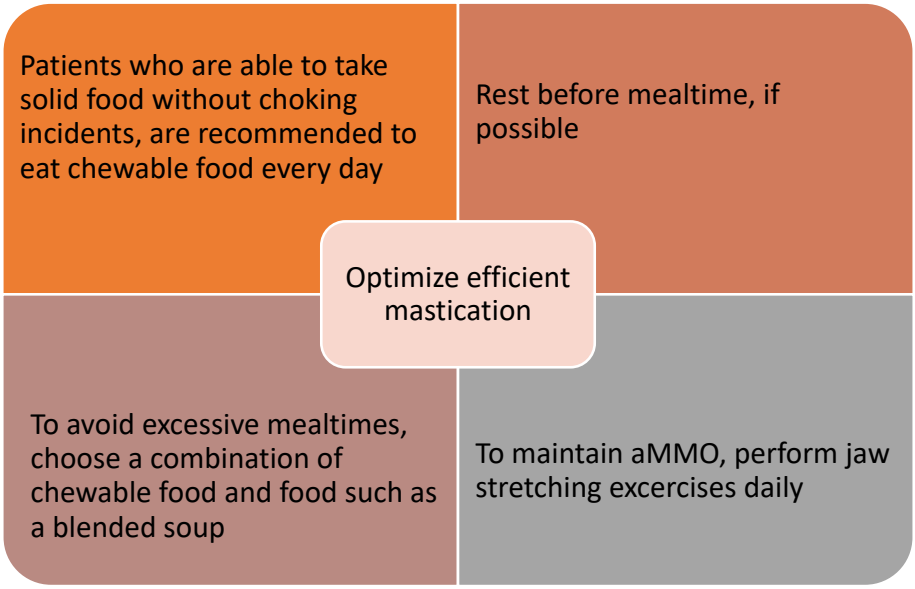

Figure 5. Recommendations to optimize efficient mastication.

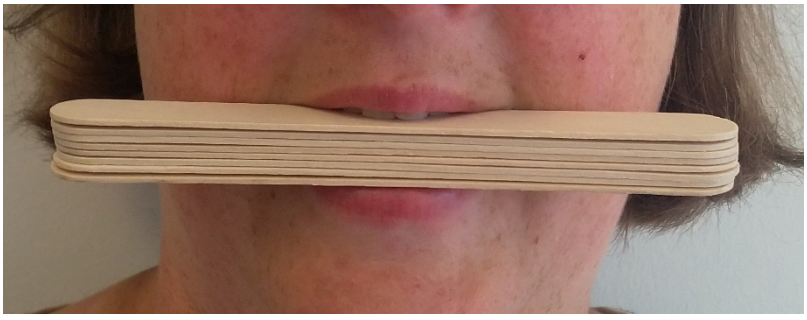

Figure 6. Jaw stretching with spatulas.

Patients who want to use a device (Therabite®) for jaw stretching, can receive support of a center for special dentistry or a physiotherapist specialized in jaw problems.

Dental malocclusions cause further deterioration of efficiency of mastication. Some patients who participated in the study in Chapter 3, had undergone orthodontics, and therefore had dentition with occlusion. As far as we know, the long-term effect of orthodontic treatment in adolescents with SMA is not known. Furthermore, studies on the effect of orthodontic treatment in other neuromuscular diseases are sparse (75-77). We found three case

reports of patients with DMD and Becker muscular dystrophy (BMD). Patients required intensive monitoring after orthodontic treatment and/or continued use of an orthodontic retainer to prevent a relapse. More research in a larger number of patients is required to assess the effect of orthodontic treatment in patients with neuromuscular diseases.

In the case of reduced masticatory endurance (i.e. fatigability), it may become increasingly difficult to cope with chewable food, resulting in excessively long mealtimes. The use of pyridostigmine (Mestinon) may improve endurance of mastication.

Facilitate efficient swallowing

If they experience coughing when swallowing liquids or solids, patients may consider small sips and bites. In addition, it is important that the patient determines the pace of eating and drinking, if they are receiving assistance.

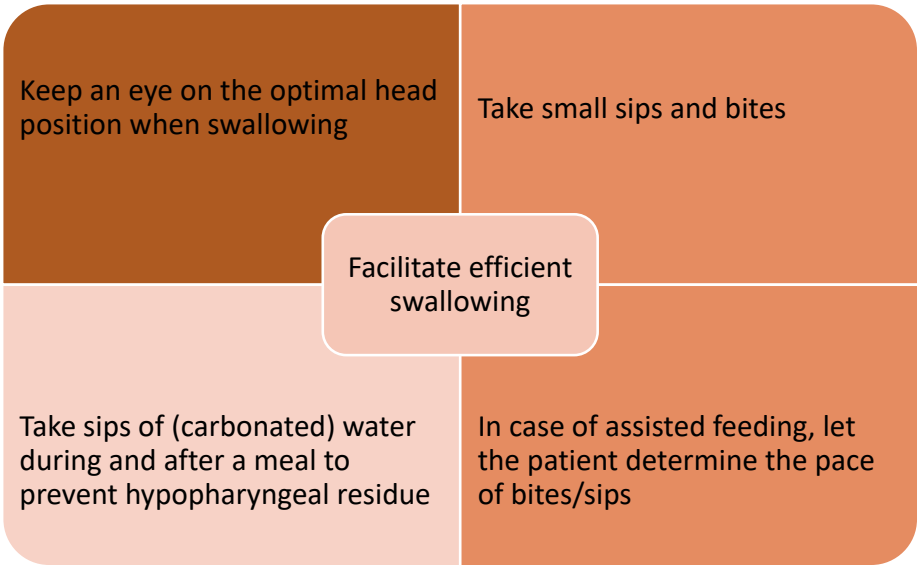

Figure 7. Recommendations to stimulate efficient swallowing.

Drinking sips of (carbonated) water during and after a meal may prevent pharyngeal residue (43, 78-80). It is not known how long pharyngeal residue remains in the hypopharynx after swallowing; this may well vary between patients. A general recommendation (to be on the safe side) is to maintain an upright posture for 30 minutes after finishing a meal (81). This can, of course, be extended if 30 minutes proves to be too short; for example, when patients still

feel residue in the throat, or when changing to a horizontal position leads to the sensation of residue releasing from the valleculae and pyriform sinuses. This is probably the best advice for now, until a better solution has been found (Figure 7).

Avoid unsafe swallowing

Swallowing difficulties may refer to unsafe swallowing (i.e. liquid or food going into the airway or blockage incidents with solid foods). We recommend that patients avoid or adapt (i.e. cut into small pieces, or puree) this food. In addition, in case of coughing with liquids or solids, consider small sips and bites. Eating mixed consistencies is not recommended, even in patients with minor mastication and swallowing problems. Consistencies such as thin soup and pieces of solid foods are difficult to control in the oral phase of swallowing, which poses a risk of choking (experiences reported by patients).

Some patients should avoid distractions, such as conversations during mealtimes, as this may provoke choking (experiences reported by patients). In case of symptoms of unsafe swallowing, the patient should ask for a swallowing function assessment, by the SLT.

Patients who use a coughing assist machine, are recommended to avoid using the device shortly after mealtime (Figure 8).

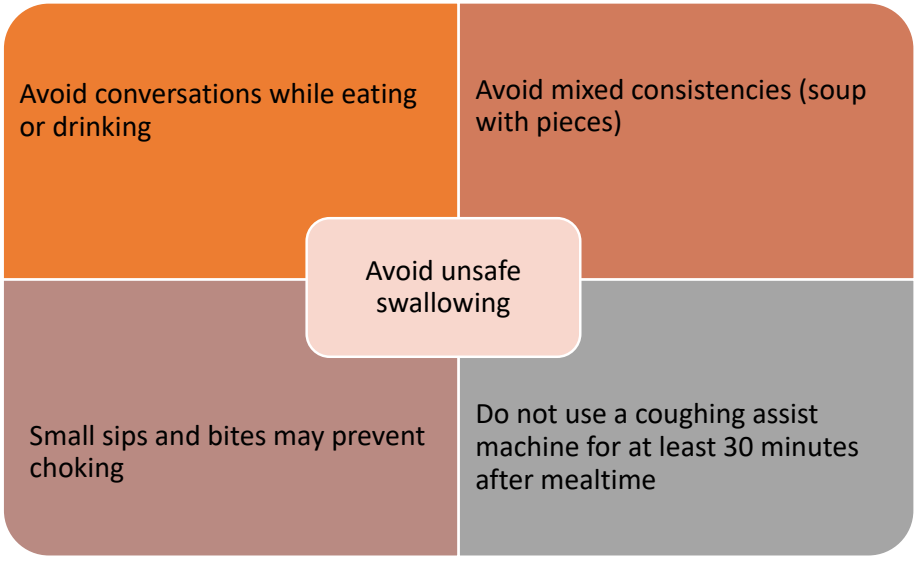

Figure 8. Recommendations to avoid unsafe swallowing.

6.3. Aim ③ To describe characteristics and symptoms of swallowing problems in infants with SMA type 1, and explore the relation with motor function.

In addition to the introduction of no less than three new treatments (*SMN*-protein augmenting drugs nusinersen, risdiplam or onasemnogene abeparvovec), a newborn screening program for SMA was implemented in the Netherlands in 2022. In the pre-screening era, children were diagnosed when symptomatic for prolonged periods of time. Our study revealed that the swallowing function of symptomatic infants treated with nusinersen deteriorated even if motor function improved (Chapter 5). Symptoms of dysphagia were often subtle and, therefore, difficult to recognize for parents and professionals. A consequence of regular aspiration is the slowly disappearing cough reaction. Aspiration irritates the airway mucosa, and results in continuous mucus production and wet breathing (Chapter 5). Following our report, other studies have described a deterioration of the swallowing function in nusinersen-treated infants. Although most infants showed an improvement of their motor function, a large proportion still had to be tube fed. In addition, the respiratory function decreased, necessitating the need for intermittent ventilatory support (82-86).

At the time of writing this thesis, infants with SMA in the Netherlands are treated with nusinersen, or onasemnogene abeparvovec (Zolgensma®) in the first weeks after birth. A recent study by McGrattan described that infants treated with onasemnogene abeparvovec, maintained bulbar function during the study period (18-24 months)(86). This study presents data of 65 symptomatic infants before the age of 6 months who participated in clinical trials of onasemnogene abeparvovec. At the end of the study, 92% of the children had no signs of a swallowing impairment and no respiratory instability. However, not all infants were assessed with a videofluoroscopic study and swallowing function was not, therefore, assessed in detail. One in four children required tube feeding suggesting significant impairments in children after gene therapy. Future studies are needed to determine in more detail the effect of onasemnogene abeparvovec and other SMA drugs on the swallowing function. Performing a VFSS directly after the treatment and on the age of 9-12 months might be considered. In addition, the timing of achievement of feeding milestones could be investigated (spoon feeding, mastication of pieces of solid food).

The care for infants with SMA type 1

In the revised professional standards of care, it is recommended that both mastication and swallowing be monitored, in children with SMA types 1 and 2 (66). In the Dutch guideline for patients with SMA type 1, it is advocated that an SLT specialized in dysphagia in infants be included in the multidisciplinary team (88). We recommend monitoring infants with SMA every 4 months. For infants receiving palliative care, symptoms of unsafe swallowing are an indication to start tube feeding immediately. In infants who are receiving one of the three treatments for SMA, VFSS should be performed in case of coughing or wet breathing during eating or drinking. A diary could be used by the parents, to record how often the infant coughs or clears the throat, while eating or drinking.

After discharge of infants with SMA and feeding problems, an SLT will visit the child at home. Goals of feeding therapy are to monitor efficient and safe swallowing, and, when feasible, to achieve feeding milestones of spoon feeding and pieces of solid foods within the first year of life.

Recommendations care for infants with SMA

The swallowing function must be monitored, both in infants with SMA being treated with one of the three therapies, and in infants who are receiving palliative care. Parents consider feeding to be an important and mutual pleasure (88). Therefore, the goal is to maintain oral feeding, provided swallowing is safe.

The following recommendations may be helpful for the feeding situation. The recommended posture during bottle/breast feeding is side-lying. A pilot study suggested that infants at risk for dysphagia demonstrated a timelier initiation of swallow and an improved coordination of swallowing when lying on their side rather than in cradled posture (90). Caregivers should avoid posturing infants with raised knees in side-lying, as this may hinder abdominal breathing.

The nipple flow must match the rate of drinking. If milk leaks from the corner of the mouth, either the nipple is allowing too fast a flow, or the infant is getting tired from drinking. Parents must be able to recognize infant's stress symptoms (for instance 'head bobbing', i.e. moving the head back and forth while drinking), that can be observed when the rate of nipple flow is too fast. Apart from the red flags reflecting unsafe swallowing, such as clearing the throat, coughing and wet breathing when eating or drinking, more subtle symptoms of unsafe swallowing are suddenly crying when drinking, or the appearance of red eyes during eating or drinking (91). These symptoms are an

indication to start tube feeding or perform a VFSS (Figure 9). Considering tube feeding also applies to the situation of increased nursing sessions, in order to achieve sufficient oral intake.

When offering solid foods, the infants is positioned in a well-supported posture with a neutral head position (92).

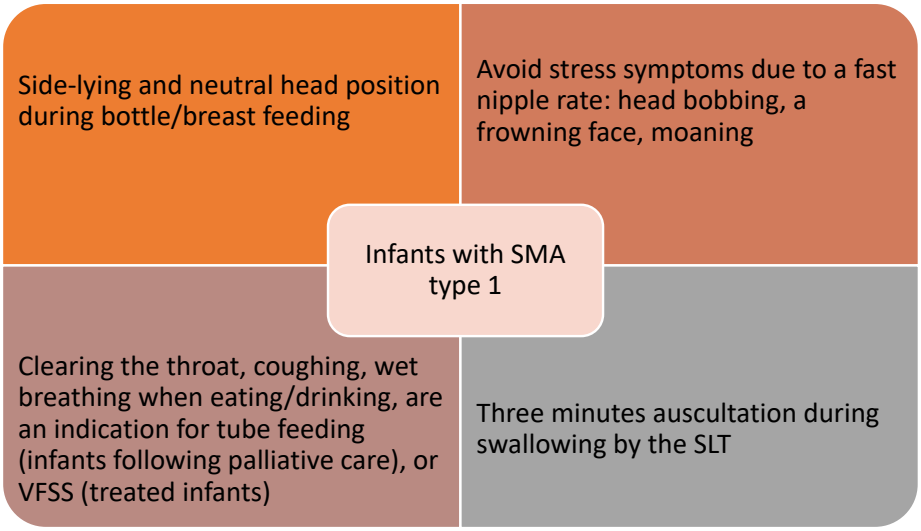

Figure 9. Recommendations for infants with SMA type 1.

6.4. Suggestions for future research

This final section contains our suggestions for future research to further unravel mastication and swallowing problems and improve care of patients with SMA.

For patients with SMA types 2 and 3 and a long disease duration, further study of the pharyngeal phase of swallowing is required. The use of manometry should be considered, in order to investigate constriction of the pharyngeal muscles, as well as pharyngo-oral regurgitation, and assess the function of the cricopharyngeal muscle during swallowing. Manometry could also be used to investigate the presence of fatigability during swallowing.

Future research is also needed to assess pharyngeal residue, in an attempt to reduce the risk of indirect aspiration. Aspects which also require

consideration are how long pharyngeal residue remains in the hypopharynx, and how this can best be cleared.

The efficacy of stretching exercises to reduce the impact of limited aMMO should be investigated.

With the introduction of (SMA) pharmacological treatments, we need biomarkers that can monitor the bulbar motor function. MRI of bulbar muscles has been used in a previous study and is described as a useful technique to document the structure of the muscle and aspects of the temporomandibular joint (9). Otto described the fact that quantitative MRI was able to detect changes in the muscles of patients with SMA, also in patients in whom there were no changes in the motor function scores (65). One might also consider investigating the bulbar function by using maximum bite force and maximum tongue pressure (93).

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Appendices

Summary

Spinal muscular atrophy (SMA, or 5q SMA) is a severe hereditary (autosomal recessive) neuromuscular disease characterized by progressive muscle weakness, loss of muscle tissue and abnormal fatigability. SMA is caused by a deficiency of the survival motor neuron (SMN) protein in (nerve) cells due to the absence of the SMN1 gene on chromosome 5q. Humans are the only animal species to possess a second SMN gene (SMN2), which differs only slightly from SMN1, but which, due to a single change in the genetic code, produces only small amounts of SMN protein. The natural variation in the number of SMN2 copies in human DNA is an important cause of the large differences in severity. More severe variants of SMA are characterized by symptoms at a (very) young age and by a lower number of SMN2 copies. Four types of SMA are distinguished, based on age at the appearance of the first symptoms and the highest achieved motor milestone (sitting independently and walking independently). SMA type 1 is the most severe and common form (an estimated 50% of new patients). In SMA type 1, the first symptoms occur between the ages of 0 and 6 months. Without treatment, these children do not achieve motor milestones such as sitting independently and most children pass away in the first year of life. Children with the mildest form of SMA type 1 who have some head balance, are classified as SMA type 1c. They have a less limited life expectancy and can reach adulthood. The first symptoms of SMA type 2 occur between 6 and 18 months and the highest motor milestone achieved by these children is sitting independently (type 2a) or standing (type 2b). When a child with SMA learns to walk, he or she is classified as SMA type 3. The first symptoms of SMA type 3 occur after the age of 18 months. In SMA type 4, the first symptoms only occur in adulthood; it is the least severe and least common form of SMA.

It is possible that the mastication and swallowing muscles are also weakened in patients with SMA. This can lead to dysphagia. Dysphagia refers to a disturbance in the swallowing process (sucking, chewing and swallowing) and this affects the safety and efficiency of swallowing*.

* Other terms used in this thesis with the same meaning as dysphagia are jaw, mastication, and swallowing problems, bulbar problems (bulbar refers to the muscles used in mastication, swallowing and speaking) or feeding problems.

As of 2016, the introduction of medications for SMA has led to an improvement in survival and some recovery of motor development in young children with SMA. At the time of writing, there are two drugs for SMA and a gene replacement therapy. The drugs are the antisense oligonucleotide nusinersen (Spinraza) and the SMN2 splicing modifier Risdiplam (Evrysdi). And the SMN1 gene replacement therapy is called onasemnogene abeparvovec (Zolgensma). Since the introduction of genetic therapies for SMA, the prognosis has improved. However, SMA cannot be cured and early detection of symptoms and rehabilitation treatment remain of great importance.

The studies in this thesis address the swallowing function of untreated children, adolescents and adults with SMA, and feeding problems in the first infants treated with nusinersen.

To date, mastication and swallowing problems in SMA have mainly been investigated using questionnaires. In the studies of this thesis we measured the mastication and swallowing function of SMA patients objectively and quantitatively and investigated the underlying causes of the mastication and swallowing problems.

The operational objectives of this thesis are:
1. Gain insight into the bulbar problems experienced by patients and their relationship with age, residual motor function and mouth opening.
2. To describe the characteristics, symptoms and underlying mechanisms of mastication and swallowing problems in adolescents and adults with SMA types 2 and 3.
3. To describe the characteristics and symptoms of swallowing problems in infants with SMA type 1 and to explore the relationship with motor function.

The aim of the research is to formulate 'best practice' advices.

Chapter 2

In Chapter 2 we described bulbar problems experienced by patients with SMA type 1-4. We invited 185 patients to complete the DDD(p)NMD (see appendix). A total of 118 patients (or their caregivers) (ages 1-75 years) participated in the study (response rate 64%).

Mastication, swallowing and speech problems were reported more often by patients with the more severe forms of SMA, while jaw problems were reported equally by patients with different SMA types. The most common reported complaints were difficulty biting off a larger piece of food (34%), fatigability

during mastication (44%), choking (56%) and a weak voice (27%). Patients with the milder forms of SMA reported increasing swallowing problems after the age of 30. Jaw, mastication and swallowing problems often occurred in combination with each. Patients reported diet modification (cutting into small pieces, pureeing or omitting food). Nevertheless, in half of the cases this did not lead to a meal duration within the acceptable standard of 30 minutes. A quarter of the patients had difficulty eating and/or drinking enough.

The level of motor functioning had hardly any influence on jaw, mastication and swallowing problems, but it did affect speech in terms of a weak voice.

In patients with SMA type 2, limited maximum mouth opening was relatively often associated with bulbar problems.

The study of Chapter 2 shows that a large proportion of patients, including older patients with the milder variant of SMA, experience bulbar problems.

Chapter 3

In Chapter 3 we described the mastication function of patients with SMA types 2 and 3. For this study we included 27 patients (including 3 ambulant patients) who experienced mastication and/or swallowing problems. The study was conducted with the DDD(p)NMD questionnaire (see appendix), clinical mastication and swallowing tests, a video fluoroscopic swallowing study, and muscle ultrasound of the bulbar muscles.

Non-ambulant patients masticated inefficiently. They needed more mastication movements and on average it took longer to eat a cracker in a standardized test. This was caused by muscle weakness and a limited maximum mouth opening, which reduced the ability of vertical and horizontal jaw movements to thoroughly grind the food. An abnormal occlusion of the teeth, caused by weak facial muscles, also contributed to the reduced mastication performance.

Another important feature was limited mastication endurance. This was caused by fatigability of the masticatory muscles. Patients had difficulty to maintain repetitive movements of mastication. In addition, they reported fatigue of the mastication muscles.

Ambulant patients had a mastication time and number of mastication movements when eating the cracker comparable to healthy subjects. There was fatigability and/or fatigue of the mastication muscles.

Muscle ultrasound of the masticatory muscles showed an abnormal muscle structure in almost all patients, both in non-ambulant and ambulant patients.

We explored the relationship between questionnaire responses and the mastication function, and found that 'diet modification' and 'experiencing mastication difficulties' were associated with a reduced masticatory efficiency. In addition, some of the patients did not notice reduced masticatory inefficiency; they answered the questions about mastication problems negatively.

Chapter 4

In Chapter 4 we described the swallowing function in the patient group as described in Chapter 3.

Non-ambulant patients swallowed inefficiently. They had a limited swallowing volume. During the video fluoroscopic swallowing study, we observed inefficient swallowing in terms of residue in the lowest part of the pharynx and an increased number of swallows when swallowing a standardized bolus. The swallowing speed (when drinking water) was on the border of normal.

We found a striking phenomenon during the video fluoroscopic swallowing study, which we described as pharyngo-oral regurgitation. The bolus was transported back to the mouth after reaching the pharynx. This phenomenon had not previously been described in patients with SMA. It is probably caused by muscle weakness in the pharyngeal phase of swallowing, resulting in an insufficient propulsion of the tongue and pharynx during swallowing.

We also assessed the safety of swallowing during the video fluoroscopic swallowing study. A quarter of the non-ambulant patients swallowed unsafely, demonstrating laryngeal penetration (down to the vocal cord level) or aspiration (beyond the vocal cords). In other words, food ended up in the airway. Remarkably, this was not accompanied by coughing. This means that unsafe swallowing in these patients can go unnoticed in daily practice.

Ambulant patients had a swallowing volume and swallowing speed for water comparable to normal subjects. We observed on the video fluoroscopic swallowing study that they swallowed the bolus with a normal number of swallows. However, residue remained in the lowest part of the pharynx.

On muscle ultrasound we observed an abnormal echogenicity of the submental and tongue muscles in the non-ambulant patients. The ambulant patients showed an abnormal echogenicity of the tongue.

Chapter 5

In Chapter 5 we described feeding problems in infants with SMA type 1.

For this study, we drew up an observation list with four domains: 1. limited endurance while eating or drinking, 2. unsafe swallowing, 3. food

regurgitation, 4. abnormalities of the respiratory system (abdominal breathing pattern and a high respiratory frequency).

Eleven infants followed palliative care. They showed characteristics of reduced endurance during feeding: they were able to drink for a short time (for example 10 minutes), but were not able to drink the recommended amount of milk (72%). To compensate, these infants were fed more frequently (55%). Some infants sweated while drinking. A striking feature was the inability to maintain the vacuum during sucking, which made drinking less efficient. Signs of unsafe swallowing were coughing when swallowing (91%), wet breath during or after feeding (64%) and throat clearing (18%). Four infants (36%) easily regurgitated feeding after tube feeding. All infants showed an abdominal breathing pattern due to muscle weakness of the respiratory muscles of the chest, and they had a high respiratory frequency.

Five infants were treated with nusinersen. The level of motor function was assessed with the CHOP INTEND (Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders) at 2, 6 and 10 months of age. All infants showed progress of the motor function after treatment with nusinersen.

Two infants had no visible symptoms of SMA at the start of treatment; motor functioning showed no abnormalities. These children had normal feeding skills. Three infants did have symptoms of SMA at the start of treatment; motor function deviated due to muscle weakness. These children showed weak sucking and wet breath while eating and/or drinking. After starting nusinersen, sucking and swallowing improved temporarily. However, between the ages of 8 and 12 months the swallowing function deteriorated. All five infants developed respiratory infections and we observed wet breathing after swallowing again. With a video fluoroscopic swallowing study we showed that wet breathing was associated with aspiration. This was an indication to start tube feeding.

The study of Chapter 5 described that the feeding situation of the infants in palliative care was associated with reduced endurance and unsafe swallowing. Infants treated with nusinersen showed progression of the motor function, a temporary progression and then deterioration of the swallowing function.

Chapter 6

In the general discussion, the underlying mechanisms of inefficient mastication, and inefficient and unsafe swallowing in patients with SMA were further elaborated. In addition, best practice advices were formulated.

There are currently guidelines (international and national) that address relatively briefly mastication and swallowing in children with SMA. A guideline

for adult care is currently not available. There is a need for this, as mastication and swallowing problems often occur in patients with SMA. Few adult patients with SMA visit a specialist with a request for help. A future guideline may include an annual check for 'red flags' such as unsafe swallowing. There is also a need for recommendations for the transfer from child to adult care.

In addition to the use of a questionnaire, we advocate the use of quantitative tests/ instruments for the assessment of mastication and swallowing problems. In addition to making a diagnosis of dysphagia, test results provide the opportunity to monitor the function of mastication and swallowing.

Recommendations for bulbar problems include adopting and maintaining the optimal body posture and head position when swallowing. We recommend to continue to use chewable food if possible. It is important not to exceed the meal times of family/friends. It may therefore be necessary to eat part of the food as (thick) liquid food. A limited maximum mouth opening may cause mastication problems. We recommend maintaining maximum mouth opening by performing stretching exercises. Drinking sips of (carbonated) water could prevent residue in the pharynx. We do not recommend eating food of a mixed consistency (soup with pieces of food). This requires extra coordination on the oral phase of swallowing and therefore poses a risk of choking. We advise patients who choke to report this to their physician and ask for a swallowing assessment.

An infant with SMA can be fed in side lying. Parents need information about the infant's stress signals during drinking, and about signals of unsafe swallowing.

Conclusion

Mastication and swallowing abnormalities are common problems in patients with SMA, and these problems require alertness from professionals. The new medical treatments for SMA are a historic breakthrough, but nevertheless we must remain aware of bulbar problems. Therefore we must continue to monitor the bulbar function of infants and children. More attention should be paid to the care of adults with SMA. Patients do not often come forward with questions about mastication and swallowing problems. The speech language therapist can help patients to reduce these problems.

Nederlandse samenvatting

Spinale musculaire atrofie (SMA, of 5q SMA) is een ernstige erfelijke (autosomaal recessieve) neuromusculaire ziekte, gekenmerkt door progressieve spierzwakte, verlies van spierweefsel en abnormale vermoeibaarheid. De oorzaak voor SMA is een tekort van het survival motor neuron (*SMN)* eiwit in (zenuw)cellen als gevolg van het ontbreken van het *SMN1* gen op chromosoom 5q. Mensen bezitten als enige diersoort een tweede *SMN* gen (*SMN2*) dat weliswaar slechts in geringe mate verschilt van *SMN1*, maar dat door een enkele verandering in de genetische code voor slechts kleine hoeveelheden SMN eiwit zorgt. De natuurlijke variatie in het aantal *SMN2* kopieën in menselijk DNA is een belangrijke oorzaak van de grote verschillen in ernst. Ernstiger varianten van SMA worden gekenmerkt door symptomen op (zeer) jonge leeftijd en door een geringer aantal *SMN2* kopieën. Er worden 4 typen SMA onderscheiden, op basis van leeftijd bij verschijnen van de eerste symptomen en de hoogst behaalde motorische mijlpaal (zelfstandig zitten en zelfstandig lopen). SMA type 1 is de meest ernstige en meest voorkomende vorm (naar schatting 50% van nieuwe patiënten). Bij SMA type 1 treden de eerste verschijnselen op tussen de leeftijd van 0 en 6 maanden. Deze kinderen behalen zonder behandeling geen motorische mijlpalen zoals zelfstandig zitten en de meeste kinderen overlijden in het eerste levensjaar. Kinderen met de mildste vorm van SMA type 1 die enige hoofdbalans hebben, worden geclassificeerd als SMA type 1c. Zij hebben een minder beperkte levensverwachting en kunnen de volwassen leeftijd bereiken.

De eerste symptomen van SMA type 2 ontstaan tussen 6 en 18 maanden en de hoogst behaalde motorische mijlpaal van deze kinderen is zelfstandig zitten (type 2a) of staan (type 2b). Wanneer een kind met SMA leert lopen, wordt het geclassificeerd als SMA type 3. De eerste verschijnselen van SMA type 3 treden na de leeftijd van 18 maanden op. Bij SMA type 4 treden de eerste verschijnselen pas op de volwassen leeftijd op; het is de minst ernstige en minst voorkomende vorm van SMA.

Ook de spieren die het kauwen en slikken mogelijk maken zijn verzwakt bij mensen met SMA. Dit kan leiden tot *dysfagie*. Dysfagie verwijst naar een verstoring van het slikproces (het zuigen, kauwen en slikken) en dit beïnvloedt de veiligheid en efficiëntie van het slikken*.

* Andere termen die gebruikt werden in dit proefschrift met dezelfde betekenis als dysfagie zijn kaak-kauw- en slikproblemen, bulbaire problemen (bulbair verwijst naar de spieren die gebruikt worden bij kauwen, slikken en spreken) of voedingsproblemen.

Vanaf 2016 heeft de introductie van medicijnen voor SMA geleid tot een verbetering van de overleving en enig herstel van motorische ontwikkeling bij jonge kinderen met SMA. Op het moment van schrijven zijn er 3 geneesmiddelen voor SMA: het antisense oligonucleotide Nusinersen (Spinraza), de SMN2-splicing modifier Risdiplam (Evrysdi) en de SMN1-gentherapie onasemnogene abeparvovec (Zolgensma). Sinds de introductie van de genetische therapieën voor SMA is de prognose dus verbeterd. SMA is echter niet te genezen en vroege signalering van symptomen en revalidatie-behandeling blijven van groot belang.

De studies in dit proefschrift gaan in op de slikfunctie van onbehandelde kinderen, adolescenten en volwassenen met SMA en over voedingsproblemen bij de eerste baby's die met nusinersen zijn behandeld.

Tot op heden werden kauw- en slikproblemen bij SMA voornamelijk met behulp van vragenlijsten onderzocht. In de studies van deze thesis hebben we de kauw- en slikfunctie van SMA patiënten objectief en kwantitatief gemeten en onderzoek gedaan naar de onderliggende oorzaken van de kauw- en slikproblemen.

De operationele doelen van dit proefschrift zijn:

1. Inzicht verkrijgen in de door patiënten ervaren bulbaire problemen en hun relatie met leeftijd, resterende motorische functie en mondopening.
2. Het beschrijven van de kenmerken, symptomen en onderliggende mechanismen van kauw- en slikproblemen bij adolescenten en volwassenen met SMA type 2 en 3.
3. Het beschrijven van de kenmerken en symptomen van slikproblemen bij baby's met SMA type 1 en het exploreren van de relatie met de motorische functie.

Het onderzoek heeft de bedoeling om 'best practice' adviezen te formuleren.

Hoofdstuk 2

In hoofdstuk 2 beschreven we bulbaire problemen die werden ervaren door patiënten met SMA type 1- 4. We nodigden 185 patiënten uit om de LINMA (Logopedisch Instrument Neuromusculaire Aandoeningen) vragenlijst in te vullen. In totaal namen 118 patiënten (of hun verzorgers) (leeftijd 1-75 jaar) deel aan het onderzoek (reactiepercentage 64%).

Kauw-, slik- en spreekproblemen werden vaker gemeld door patiënten met de ernstigere vormen van SMA, terwijl kaakproblemen door mensen met verschillende SMA typen in gelijke mate werden gerapporteerd. De meest

voorkomende klachten die werden gemeld waren problemen met het afbijten van een groter stuk voedsel (34%), snel optredende vermoeibaarheid bij kauwen (44%), verslikken (56%) en een zwakke stem (27%). Bij patiënten met de mildere vormen van SMA viel op dat zij na de leeftijd van 30 jaar relatief veel slikproblemen meldden. Kaak-, kauw- en slikproblemen kwamen vaak in combinatie met elkaar voor. Patiënten pasten hun dieet aan (het in kleine stukjes snijden, pureren of weglaten van voeding). Desondanks leidden deze aanpassingen in de helft van de gevallen niet tot een maaltijdduur binnen de aanvaardbare norm van 30 minuten. Een kwart van de patiënten had moeite om voldoende te eten en/of te drinken.

Het niveau van motorisch functioneren was nauwelijks van invloed op de kaak-, kauw-, en slikproblemen, maar wel op spreekproblemen in de vorm van onvoldoende stemvolume.

Bij patiënten met SMA type 2 ging een beperkte maximale opening van de mond relatief vaak samen met bulbaire problemen.

De studie van hoofdstuk 2 toonde aan dat een groot deel van de patiënten, inclusief oudere patiënten met de mildere variant van SMA, bulbaire problemen ervaart.

*

Hoofdstuk 3

In hoofdstuk 3 beschreven we de kauwfunctie van patiënten met SMA type 2 en 3. Voor deze studie includeerde we 27 patiënten (waaronder 3 patiënten die konden lopen) die kauw- en/of slikproblemen ervaarden. Het onderzoek werd uitgevoerd met de vragenlijst LINMA (zie appendix: DDD(p)NMD), klinische kauw- en sliktests, röntgenslikonderzoek en spierechografie.

Rolstoel gebonden patiënten kauwden inefficiënt. Zij hadden meer kauwbewegingen nodig en het duurde gemiddeld langer om een cracker te eten in een gestandaardiseerd testje. Oorzaken waren spierzwakte en een beperkte mondopening, waardoor minder goede verticale en horizontale kaakbewegingen mogelijk zijn om de voeding grondig te vermalen. Ook een abnormale stand (occlusie) van het gebit, veroorzaakt door zwakke spieren van het gezicht, droeg bij aan de verminderde kauwprestaties.

Een ander belangrijk kenmerk was een beperkt uithoudingsvermogen om te kauwen. Dit werd veroorzaakt door een snelle vermoeibaarheid van de kauwspieren. Patiënten hadden moeite om de herhalende beweging van het kauwen vol te houden. Daarnaast meldden zij een vermoeid gevoel in de kauwspieren.

Bij de patiënten die konden lopen was de kauwduur en het aantal kauwbewegingen bij het eten van de cracker vergelijkbaar met gezonde proefpersonen. Er was wel sprake van vermoeibaarheid en/of vermoeidheid van de kauwspieren.

Spierechografie van de kauwspieren toonde een abnormale spierstructuur aan in bijna alle patiënten, zowel bij rolstoel gebonden als lopende patiënten.

Bij het onderzoeken van de relatie tussen de antwoorden van de vragenlijst en de kauwfunctie, bleek het melden van dieetmodificatie en het ervaren van kauwmoeilijkheden samen te hangen met verminderde kauwprestaties. Daarnaast bleek een deel van de patiënten niet te merken dat zij inefficiënt kauwden, want zij beantwoordden de vragen over kauwproblemen ontkennend.

Hoofdstuk 4

In hoofdstuk 4 beschrijven we de slikfunctie in de patiëntgroep zoals beschreven in hoofdstuk 3.

Rolstoel gebonden patiënten slikten inefficiënt. Zij hadden een beperkt slikvolume. Bij röntgenslikonderzoek observeerden we inefficiënt slikken in de vorm van restjes voeding in het laagste deel van de keelholte en was er een verhoogd aantal slikken nodig om een gestandaardiseerde bolus weg te slikken. De sliksnelheid (bij het drinken van water) was op de rand van normaal.

We vonden bij röntgenslikonderzoek een opvallend fenomeen, dat we omschreven als faryngo-orale regurgitatie. Hierbij werd de voedselbrok na het bereiken van de keelholte (farynx) weer terug getransporteerd naar de mond. Dit verschijnsel was niet eerder beschreven bij mensen met SMA. Waarschijnlijk wordt dit veroorzaakt door spierzwakte in de faryngeale fase van het slikken, waardoor de stuwende kracht van de tong- en keelspieren onvoldoende is om de bolus weg te slikken.

Met röntgenslikonderzoek beoordeelden we ook de veiligheid van het slikken. Een kwart van de rolstoel gebonden patiënten had een onveilige slik waarbij laryngeale penetratie tot op stembandniveau of aspiratie (voorbij de stembanden) optrad. Dit houdt in dat er voeding in de luchtweg belandde. Opvallend genoeg ging dit niet gepaard met een hoestreactie. Dit betekent dat in de dagelijkse praktijk onveilig slikken bij deze patiënten onopgemerkt kan blijven.

Lopende patiënten hadden een normaal slikvolume en sliksnelheid voor water. Bij röntgenslikonderzoek slikten zij de bolus door met een normaal

aantal slikken, maar er bleven wel resten voeding achter in het laagste deel van de keelholte.

Spierechografie toonde een abnormale echogeniciteit van de mondbodem en tongspieren bij de rolstoel gebonden patiënten. Bij de lopende patiënten was er enkel een abnormale echogeniciteit van de tong.

Hoofdstuk 5

In hoofdstuk 5 beschrijven we voedingsproblemen bij baby's met SMA type 1.

Voor deze studie stelden we een observatielijst op met 4 domeinen: 1. beperkt uithoudingsvermogen bij eten of drinken, 2. onveilig slikken, 3. regurgitatie van voeding, 4. abnormaliteiten van het ademhalingsstelsel (buik-adempatroon en hoge ademfrequentie).

Elf baby's volgden een palliatief traject. Zij vertoonden in de voedingssituatie kenmerken van een verminderd uithoudingsvermogen: zij konden kort drinken (bijvoorbeeld 10 minuten) waarin zij niet de aanbevolen hoeveelheid voeding dronken (72%). Ter compensatie werden deze baby's frequenter gevoed (55%). Sommige baby's transpireerden tijden het drinken. Een opvallend kenmerk was het niet kunnen volhouden van het vacuüm tijdens het zuigen, waardoor het drinken minder efficiënt verliep. Signalen van onveilig slikken waren hoesten bij slikken (91%), natte adem tijdens of na de voeding (64%) en keelschrapen (18%). Vier kinderen (36%) gaven gemakkelijk voeding terug na het krijgen van sondevoeding. Alle kinderen vertoonden een buik-adempatroon door spierzwakte van de ademhalingsspieren van de borstkas en zij hadden een hoge ademfrequentie.

Vijf baby's werden behandeld met nusinersen. Het niveau van het motorisch functioneren werd bepaald met de CHOP INTEND (Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders), op de leeftijd van 2, 6 en 10 maanden. Alle baby's toonden een motorische vooruitgang na de behandeling met nusinersen.

Twee baby's hadden nog geen zichtbare symptomen van SMA bij aanvang van de behandeling; het motorisch functioneren vertoonde geen afwijkingen. Deze kinderen hadden normale voedingsvaardigheden. Drie baby's hadden wel symptomen van SMA bij aanvang van de behandeling; het motorisch functioneren week af door spierzwakte. Deze kinderen toonden zwak zuigen en een natte adem tijdens eten en/of drinken. Na de start met nusinersen verbeterde het zuigen en slikken tijdelijk. De slikfunctie ging echter achteruit tussen de leeftijd van 8 en 12 maanden. Alle vijf baby's kregen luchtweginfecties en we observeerden opnieuw de natte adem na het slikken.

Met röntgenslikonderzoek toonden we het verband aan tussen een natte adem en aspiratie. Dit was een dus een indicatie om sondevoeding te starten.

De studie van hoofdstuk 5 beschreef dat de voedingssituatie van de kinderen in het palliatieve traject gepaard ging met verminderd uithoudingsvermogen en onveilig slikken. Bij de met nusinersen behandelde kinderen was er wel een motorische vooruitgang, een tijdelijke vooruitgang en vervolgens een achteruitgang van het slikken.

Hoofdstuk 6

In de algemene discussie werden de onderliggende mechanismen van inefficiënt kauwen, en inefficiënt en onveilig slikken van patiënten met SMA verder uitgewerkt. Daarnaast werden aanbevelingen voor de zorg gedaan en adviezen gegeven.

Op dit moment zijn er redelijk summiere richtlijnen (internationale en nationale) die ingaan op kauwen en slikken bij kinderen met SMA. Een richtlijn voor deze zorg voor volwassenen ontbreekt tot op heden. Hier is wel behoefte aan, aangezien kauw- en slikproblemen vaak voorkomen bij SMA. Weinig volwassen patiënten met SMA bezoeken een specialist met een hulpvraag. In de toekomstige richtlijn kan worden opgenomen dat er een jaarlijkse check moet zijn op 'rode vlaggen' zoals onveilig slikken. Ook is behoefte aan aanbevelingen voor de transfer van kinder- naar volwassenzorg.

Naast het gebruik van een vragenlijst pleiten wij voor het gebruik van kwantitatieve onderzoeken/ instrumenten voor de beoordeling van kauw- en slikproblemen. Hiermee kan de diagnose dysfagie worden gesteld en het geeft de mogelijkheid om de kauw- en slikfunctie te volgen.

Adviezen voor bulbaire problemen omvatten het aannemen en volhouden van de optimale houding bij het slikken. We adviseren om, indien mogelijk, kauwbare voeding te blijven gebruiken. Hierbij is het belangrijk om de maaltijdduur van familie/vrienden aan te houden. Het kan dus nodig zijn een deel van de voeding in een (dik-)vloeibare vorm te eten. Kauwproblemen kunnen ontstaan door een beperkte maximale mondopening. We raden aan om de maximale mondopening op peil te houden door stretchoefeningen. Het drinken van slokjes (koolzuurhoudend) water zou residu in de keelholte kunnen voorkomen. We raden af om voeding van een gemengde consistentie (soep met stukjes) te eten, omdat dit een extra beroep doet op de orale controle en dus een risico vormt op verslikken. Patiënten die zich verslikken adviseren we dit te melden bij de arts en te vragen om een slikonderzoek.

Een baby met SMA kan in zijligging gevoed worden met de borst of fles. Ouders hebben behoefte aan informatie over stresssignalen van de baby tijdens drinken, en over signalen van onveilig slikken.

Conclusie

Kauw- en slikafwijkingen zijn een bekend probleem bij patiënten met SMA en dit vraagt om alertheid bij professionals. De nieuwe medicamenteuze behandelingen voor SMA zijn een historische doorbraak, maar desondanks moeten we alert blijven op bulbaire problemen. Dit betekent dat we de bulbaire functie van baby's en kinderen moeten blijven volgen. Er dient meer aandacht te komen voor de zorg voor volwassenen met SMA. Deze patiënten vragen weinig hulp voor kauw- en slikproblemen. De logopedist kan helpen bij het vinden van een aanpak om deze problemen te verminderen.

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*

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Curriculum vitae

Anne Marise Barbara van der Heul is geboren op 31 mei 1962. Na de middelbare school (HAVO) volgde Marise de opleiding tot verpleegkundige A in het Diaconessenhuis te Eindhoven. Na haar opleiding ging zij als verpleegkundige werken in het Wilhelmina Kinderziekenhuis te Utrecht en behaalde haar kinderaantekening. Hoewel zij zich thuis voelde op deze werkplek, bleef zij zoeken naar een andere invulling van haar toekomstige werk. In 1986 startte zij met de opleiding logopedie te Utrecht. In 1990 studeerde zij af en richtte een praktijk voor logopedie op waarin zij aanvankelijk zowel met kinderen als volwassenen werkte, maar zich later op preverbale logopedie richtte. Daarnaast werkte zij bij Bartimeus op de Bosschool voor kinderen met een meervoudige visuele beperking. Zij volgde de Neuro Developmental Treatment (NDT) opleiding, en prelogopedie Muller opleiding. In 1998 werkte zij in de Hoogstraat op de afdeling kinderrevalidatie. Hier werkte zij met kinderen van 0 -5 jaar aan de communicatie en eet- en slikproblemen.
In 2000 begon zij in het Meander Medisch Centrum op de afdeling kinderrevalidatie en werkte daar ook op de kinderafdeling en neonatologie in de kliniek. In 2008 werd haar werkplek het Wilhelmina Kinderziekenhuis te Utrecht waarbij zij betrokken was bij diagnostiek en behandeling van eet-en slikproblemen en spraaktaalproblemen.
Vanaf 2018 breidde zich dit uit met het Prinses Maxima Centrum voor kinderoncologie. Hier specialiseerde zij zich verder in eet- en slikproblemen bij kinderen van 0 – 18 jaar. In 2014 rondde zij de master evidence based practice af aan de Universiteit van Amsterdam, waarvoor zij een vragenlijst ontwikkelde voor baby's die wennen aan lepelvoeding. Vanaf 2016 begon zij aan het project Eet SMA-kelijk, waaruit dit proefschrift is ontstaan.
Marise is getrouwd met Frans Stuyt en zij hebben drie kinderen.

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DDD(p)NMD

Diagnostic list for Dysphagia and Dysarthria in (pediatric) Patients with Neuromuscular Diseases (DDD(p)NMD)

Are you often ill as a result of swallowing problems ?	Yes - No
Do you suffer from respiratory infections?	Yes - No
Do you use antibiotics on a long-term basis?	Yes - No
Do specific foods cause problems with swallowing?	Yes - No

Swallowing problems:

- ▫ never occur;
- ▫ occur with solid foods;
- ▫ occur with pureed food and thick liquids;
- ▫ occur both with liquids and solid foods.

Do you dread mealtimes?	Yes - No
Do you sometimes refuse food?	Yes - No
Do you adapt food, for instance by cutting it into small pieces, pureeing it or avoiding hard foods?	Yes - No
Do you experience difficulty with chewing?	Yes - No
Do your jaws get tired when chewing?	Yes - No
Do mealtimes take a long time (longer than 30 minutes)?	Yes - No
Do you tend to choke ('yes' if you choke more than once a day)	Yes – No
Do you tend to gag or vomit?	Yes – No
Do you cough when swallowing solid foods?	Yes – No
Do you cough when swallowing liquids?	Yes - No
Do you feel as if food is sticking in your throat?	Yes - No

The feeling of food sticking in the throat:

- ▫ Does not occur;
- ▫ Occurs with solid foods;
- ▫ Occurs with pureed and thick liquids;
- ▫ Occurs with both liquids and solid foods.

Do you experience excessive burping?	Yes - No
Do you get tired when eating?	Yes - No
When you eat do you tend to drool?	Yes - No
Is your mouth often open?	Yes - No
Is your mouth opening limited for brushing teeth?	Yes - No
Do you experience jaw problems with biting off a large piece of food?	Yes – No
Do you experience jaw problems with biting off hard foods ?	Yes – No
Do you experience jaw problems when yawning?	Yes – No
Do you experience jaw problems when laughing?	Yes – No
Do you experience jaw problems when you are tired?	Yes – No
Do you experience jaw problems when you are waking up?	Yes – No
Is your daily intake for solid foods sufficient?	Yes - No
Is your daily intake of liquids sufficient?	Yes - No
Do you make (partial) use of tube feeding?	Yes - No
Are you gaining too much weight?	Yes - No
Are you losing weight?	Yes - No
Is your weight too low	Yes - No
Is (or was) a dietician involved?	Yes - No
Do you suffer from shortness of breath when talking?	Yes – No
Do you get tired when talking?	Yes – No
When you talk to people, do they ask you to repeat what you said?	Yes – No
Do people have problems understanding you when you are talking in a noisy environment?	Yes – No
Do you suffer from a sore throat due to talking?	Yes – No
Is your voice loud enough?	Yes - No

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