Mandibular function in neuromuscular disorders

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Chapter 1

General introduction

Introduction

Neuromuscular disorders (NMDs) are defined as a wide range of syndromes and diseases affecting the muscles and their nervous control. The most frequent symptoms are muscle weakness and fatigue. Two of the most common types of neuromuscular disorders are spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD).

Children and adults with NMD often report problems with feeding and swallowing.[1-3] A feeding disorder is defined as a problem with eating activities like bringing a spoon to the mouth, selectivity or avoidance of food or mastication. A swallowing disorder or dysphagia is defined as a disorder in one or more phases of the swallowing process; the oral, the pharyngeal or esophageal phase. The overall prevalence of feeding disability reported by patients with NMD is 34%.[1] In the face of the serious consequences of muscle weakness and fatigue in general, these may seem minor problems. However, difficulties with mastication and swallowing can adversely affect health, both directly and indirectly. Poor mastication in combination with weak pharyngeal clearance may increase pharyngeal post swallow residue and may cause complications, e.g. choking or the feeling of sticking food in the throat.[4] In addition, problems with feeding can have a psychological aspect like embarrassment and social isolation and this can adversely affect quality of life.[5] As a consequence patients may for example try to avoid prolonged feeding times, which may lead to inadequate nutrition and an increased rate of disease progression.[6,7]

In patients with SMA and DMD, the orofacial muscles are often affected. This may cause specific abnormalities in mandibular function and in the craniofacial morphology, shape of the dental arches and the dental occlusion.[8-16] The mechanisms that cause impairment of mandibular function in SMA and DMD are poorly understood. Fatty degeneration of muscle fibers, causing stiffness and weakness of the masticatory muscles (mouth openers and closers), and reduced head balance may have an effect on the mandibular function.

As each NMD has its distinct pathology and characteristics, each disorder may have a different impact on the masticatory system. To be able to develop disease-specific recommendations, it is necessary to study the underlying mechanisms of impaired mandibular function in SMA and DMD. Treatment of the mandibular dysfunction depends on insight in these mechanisms.

The focus of this thesis is on SMA and DMD as two major and distinct classes of NMDs. The primary aim is to explore the impact of SMA and DMD upon aspects of mandibular function of patients with SMA and DMD focusing on mastication and mandibular mobility. The second aim is to establish whether the differences in pathophysiology and

clinical presentation of SMA and DMD cause distinct patterns of compromised mastication. A third aim is to investigate whether specific training advice influences mandibular function in DMD.

In this introduction, NMD in general, SMA, DMD and the masticatory system specifically will be discussed and the outline and the operational aims of this thesis will be described.

Neuromuscular disorders

NMDs have an impact on the central or the peripheral nervous system and are characterized by progressive muscle weakness with variable distribution and severity. According to the distribution of the predominant muscle weakness and the location of the defects, the major NMDs can be classified into four main groups (Table 1.1).[17]

Table 1.1. Classification of the major neuromuscular diseases, adapted from Dubowitz, 1996.[17]

NMD	Defects	Most common diseases
Motor neuron diseases	Lower motor neurons[a] and sometimes upper motor neurons[b]	Amyotrophic lateral sclerosis **Spinal muscular atrophy**
Neuropathies	Peripheral nervous system is affected	Charcot-Marie-Tooth disease Hormonal disorder diabetes
Neuromuscular junction disorders	Transmission of the signal to muscle contraction is blocked	Myasthenia gravis
Myopathies incl. muscular dystrophies	Forestall the maintenance and repair of muscle tissue	Becker muscular dystrophy **Duchenne muscular dystrophy** Congenital muscular dystrophy

[a]Lower motor neuron: a motor neuron whose cell body is located in the brainstem or the spinal cord and whose axon innervates skeletal muscle fibers; [b]Upper motor neuron: a motor neuron whose cell body is located in the motor area of the cerebral cortex and whose processes connect with motor nuclei in the brainstem or the anterior horn of the spinal cord.

NMDs are likely to affect the masticatory system as well. Feeding disorders, reported by patients with NMD, may be secondary to progressive weakness of the masticatory muscles. Mastication problems may induce post swallow residue, which has been suggested to contribute to a greater risk of food aspiration.[18,19] Furthermore, a common problem in many

NMDs is dysphagia expressed as a difficulty in inhaling and exhaling and consequently with coughing. Therefore, the complications of swallowing disorders can be devastating, including aspiration and pneumonia and may ultimately lead to death.[3,20,21]

Spinal muscular atrophy

SMA is a recessive neuromuscular disorder caused by the homozygous deletion of the survival motor neuron (SMN) 1 gene that has been mapped to chromosome 5q11.2–13.3.[20,22]

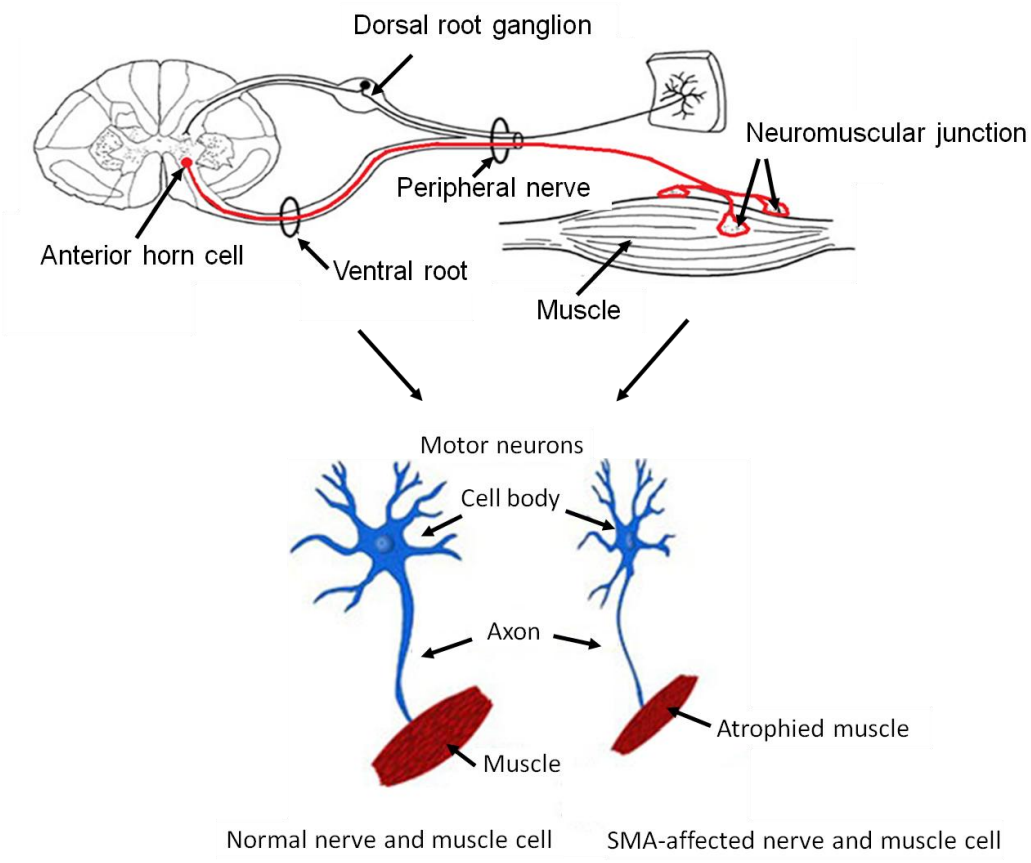

Figure 1.1. Spinal muscular atrophy and degeneration and loss of the motor neurons in the anterior horn cells in the spinal cord (see red dot) and the brain stem nuclei, resulting in a reduction of nerve signals from the motor neurons to bunches of muscle fibers (see red line). Reduced signals to muscle fibers cause atrophy and weakness of muscles used for activities such as controlling head movement.
(Figure adapted from www.stemcellthailand.org and www.neuroanatomy.wisk.edu)

SMN 1 is critical to the function and survival of motor neurons. An absence or shortage of SMN 1 leads to degeneration of the lower motor neurons in the spinal cord, causing predominantly progressive proximal muscle weakness (Figure 1.1).[21,22] As a result, activities such as walking and sitting are affected; in the more severe types, the muscles used for breathing and swallowing are affected as well. With an incidence of about 1:6.000 to 1:10.000

it is one of the most common autosomal recessive diseases and an important hereditary cause of childhood morbidity.[23,24]

SMA severity varies considerably, and age at onset and maximum motor function achieved are used to distinguish 4 subgroups (Table 1.2). Patients with SMA type 1 (Werdnig-Hoffmann disease) have disease onset before the age of 6 months and never learn to sit. Patients with SMA type 2 have an onset before the age of 18 months and never learn to stand or walk. Patients with SMA type 3 (Kugelberg-Welander disease) and adult onset type 4 with onset after the age of 18 months and 30 years, respectively, are able to learn to walk.[22,25-28] Additionally SMA type 3 can be divided into type 3a with an onset before 3 years and type 3b with an onset after the age of 3 years. [26]

Table 1.2. Classification of spinal muscular atrophy, adapted from Munsat and Davies, 1992.[25]

	SMA type 1	SMA type 2	SMA type 3	SMA type 4
Severity	Severe	Intermediate	Mild	Mildest
Age of onset	< 6 months	< 18 months	18-36 months	30 years
Highest function	Never sits	Sits, never stands	Stands, walks	Walks
Life expectancy	< 2 years	> 2 years	Adult	Adult

Orofacial consequences

Patients with SMA or their caretakers often report mastication difficulties, limited mouth opening, and swallowing difficulties. However, only few studies have systematically investigated these issues.[1,3,16] It has been suggested that reduced mandibular range of motion (ROM), weakness of the masticatory and tongue muscles, limited efficiency of the movement of the tongue, abnormal craniofacial growth patterns and dental malocclusions in patients with SMA may lead to a compromised masticatory performance.[8,11,29] A low masticatory performance may result in less fragmentation of food. Less fragmentation of food may increase post swallow residue.[18,30] Video fluoroscopic swallow studies showed an increased pharyngeal post swallow residue of solid food in advanced stages of SMA.[4,18,30] When large amounts of residue remain post swallow, the risk for aspiration is increased when the patient inhales after the swallow and the airway opens naturally.[30-32]

To our knowledge no objective assessments using masticatory performance tests in SMA have been described in the literature. The mechanism behind the limitations of the mandibular function is unclear and to our knowledge predictive factors for a compromised mandibular ROM have not been investigated yet.

Duchenne muscular dystrophy

DMD is characterized by a progressive loss of muscle cells and replacement by fat and connective tissue.[33] DMD is an X-linked recessive disorder or, in one-third of all cases, a consequence of *de novo* gene mutation. Female carriers have no symptoms. It is caused by a defective gene for dystrophin, an essential component of the dystrophin–glycoprotein complex (DGC) maintaining the membrane integrity of muscle fibers (Figure 1.2).[34] As the disease progresses and destroyed muscle fibers are removed by macrophages, fatty and connective tissue will fill the empty spaces and muscle pseudohypertrophy will appear.[35] DMD is affecting eventually all voluntary muscles including the heart and breathing muscles. With an incidence of about 1: 3500 live male births it is the most prevalent type of muscular dystrophy in children.[36] The onset of DMD symptoms occurs at around 2 to 6 years of age. By 3-4 years of age most boys with DMD show difficulty climbing stairs or rising from a seated position on the floor. Enlargement of the calf muscles (pseudohypertrophy or hypertrophy) is common. When the condition is not treated, muscle strength deteriorates, and boys require the use of a wheelchair before their teens.[37] Learning disability and neurobehavioral problems are present in about 30% of boys and young men with DMD.

Orofacial consequences

There are reports that the weakness of the craniofacial muscles and the tongue muscles in DMD consequently affect the development and morphology of craniofacial structures.[10,12-15,38] Weakness of the jaw muscles, in combination with changes in the craniofacial morphology may impair mandibular function, including masticatory performance and mandibular range of motion.[39] Dental abnormalities like delayed eruption of the permanent dentition, agenesis, microdontia, and hypoplasia typically of premolars may occur and may influence mastication.[12,40,41] To our knowledge, masticatory performance so far has not been assessed objectively using masticatory performance tests. Hence it is still unclear which factors influence the mandibular function in these patients.

Patients with DMD are at risk for dental caries, gingivitis and periodontal disease because of heavy plaque and calculus deposits. The increased deposits are mainly caused by

loss of muscle function of the arms and hands, reduced mouth opening and dental abnormalities, weakness of the masticatory muscles, macroglossia and weakness of the tongue muscles resulting in poor clearing of food and liquids from the mouth. [3,12,14,15, 38-40,42,43]

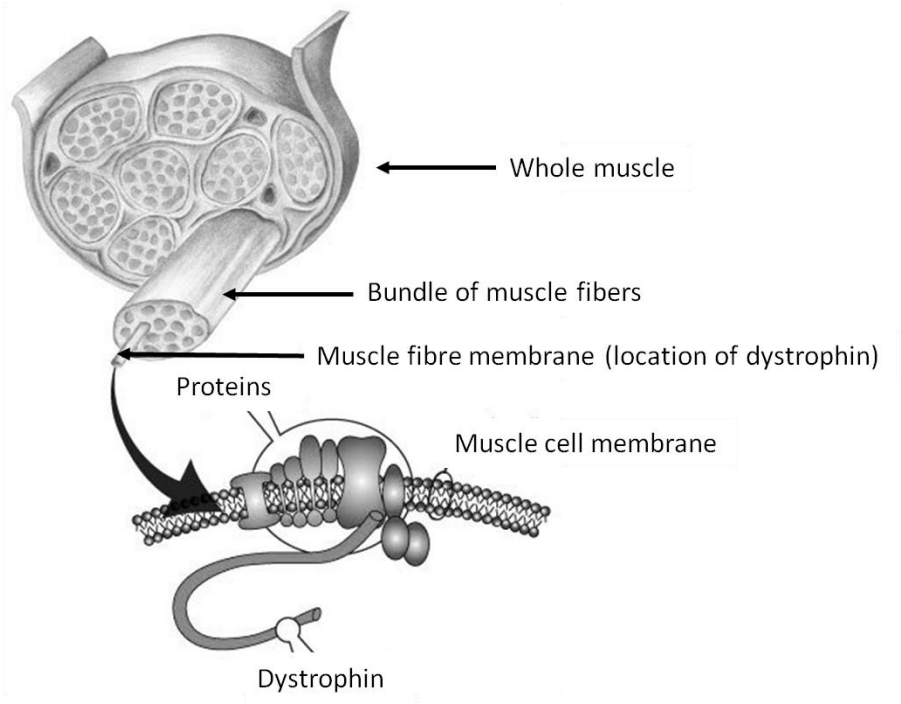

Figure 1.2. The protein dystrophin is located on the cytoplasmic surface of skeletal muscle cell membranes and forms a mechanical link between the axtin filaments inside the muscle cells and the extacellular matrix. Dystrophin has a major structural role in mechanical stability during muscle contractions.[34]
(Figure adapted from www.mda.org)

Mandibular function

Functional outcomes of the masticatory system can be measured in terms of e.g. the masticatory performance, maximal voluntary bite force and mandibular range of motion.[44] The dominant factors influencing masticatory performance in healthy subjects are the number of occlusal contacts in the (pre)molar regions and the bite force.[45] Furthermore, tongue function is of importance because of its role in food-bolus formation and positioning.[46] Mastication, the process of chewing food before swallowing and digestion, is considered to be a part of the oral phase of swallowing. The food is prepared into a bolus by (1) breaking large pieces of food into small pieces, (2) softening of food and transformation into a size conducive to swallowing, and (3) lubrication of food by impregnating it with saliva.[47] All components of the masticatory system, such as the teeth and their surrounding structures, masticatory muscles, temporomandibular joints, lips, cheeks, palate, and the tongue are

involved. During mastication, the mandible moves not only vertically, but also anteroposteriorly and laterally.[48]

Bite force is one indicator of the functional state of the masticatory system that results from the action of jaw elevator muscles.[49] Many factors like the dimensions of the masticatory muscles, dental occlusion, facial morphology, and pain during functional, influence the bite force magnitude.[50] The great variation in bite force values depends on these factors, but also on e.g. the physiological characteristics of the subject, the motivation of the patient and the mechanical characteristics of the bite force transducer.[51] Comparing the bite force values within the literature must take place carefully.[50]

The temporomandibular joint (TMJ) plays an important role in mandibular function. The TMJ is a synovial bi-articular, hinge-type joint and contains a fibrocartilaginous articular surfaces and disc dividing each joint into an upper and lower joint cavity. Movement in the upper joint compartment is mostly sliding of the mandibular condyle, whereas in the lower joint compartment rotation is predominant.

Masticatory muscles and the supra- and infrahyoid muscles are responsible for the various mandibular movements (Table 1.3). The most important influencing factors upon the mandibular ROM in healthy subjects are the length of the mandible, functional capacity of the mandibular opening and closing muscles, morphology and status of the TMJ, and pain conditions in the masticatory system.[52,53]

Table 1.3. Mandibular movements and the muscles primarily involved

Mandibular movements	Muscles in action
Opening (depression)	Lateral pterygoid; suprahyoid; infrahyoid
Closing (elevation)	Temporalis; masseter; medial pterygoid
Protrusion	Lateral pterygoid; masseter (superficial fibers); medial pterygoid
Retrusion	Temporalis; masseter (deep fibers)
Lateral	Temporalis ipsilateral; lateral pterygoid; contralateral; masseter

The following movements of the mandible are distinguished:[54-57]
(1) opening: as the jaw opens, the mandibular elevators, i.e., masseter, temporalis, and medial pterygoid muscles, relax and allow gravity to assist. When opening against resistance (e.g., tension in the mouth closing muscles), the suprahyoid muscles contract while the infrahyoid muscles stabilize the hyoid bone. In mouth opening, rotation of the condyle inside the TMJ

between the disk and the condylar head in both joints dominates. The rotation movement allows a partial opening of approximately 20 to 25 mm, measured between the incisal edges of the anterior teeth. The second type of movement in the TMJ is a sliding movement of the condyle and disk along the articular eminence of the temporal bone. This movement occurs through contraction of the lateral pyterygoid muscle, which are pulling the condyle anteriorly. Both rotation and sliding must occur for the jaw to fully open.
(2) closing: jaw closure or mandibular elevation is accomplished through contraction of the mandibular elevators and retraction of the disc by the elastic fibers of the upper stratum of the bilaminar zone.
(3) protrusion: protrusion occurs by contraction of the lateral and medial pterygoid muscles and the masseter muscles on both sides. The lateral pterygoid muscles cause the condyles and the articular discs to slide anteriorly along the articular eminence of the temporal bone.
(4) retrusion: during retrusion, the disks and condyles slide posteriorly with the condyles in the joint cavities which is accomplished by the temporalis muscles (posterior fibers).
(5) mandibular range of motion: lateral movements occur through simultaneous contraction of the temporalis and digastric muscle on the ipsilateral side and the lateral pterygoid and superfacial masseter muscle on the contralateral side.

Assessment of mandibular function

Mandibular function can be assessed subjectively through self-report, or objectively by performing a clinical examination or a combination of both.[58] In this thesis we applied the latter approach by using questionnaires as well as clinical examination.

The questionnaire Screen was designed to assess pain in the head and neck region, and mandibular function and related issues.[59,60] Mandibular Functional Impairment Questionnaire (MFIQ) was designed to measure impairments of the function of the masticatory system.[61]

Further, the participants in our studies were clinically examined following the validated procedure as described by Lobbezoo-Scholte et al. (1993, 1994).[62,63] Clinical examination consisted of: history taking of the main complaints; the current and experienced limitations of mandibular function; the dental, medical, and personal history of the patient; an extra-oral inspection of the head and neck; and an intra-oral inspection of the dentition and the soft tissues.

Additionally the impact of neuromuscular disease on the masticatory system was assessed by measuring the anterior maximum voluntary bite force (MVBF) with the VU University Bite Force Gauge (VU-BFG) and the masticatory performance using the mixing

ability test.[64,65]

We combined the dental data from our patient groups with the medical information (i.e., medication, body height, body length, ventilation support), general physical abilities and quantitative muscle ultrasound imaging (QMUS) of the tongue and the suprahyoid muscles. For the assessment of the general physical ability at the department of Rehabilitation, Radboud university medical center the Motor Function Measure (MFM) was used and at the department of Neurology and Neurosurgery and Spieren voor Spieren Kindercentrum, Brain Center Rudolf Magnus, the Hammersmith functional motor scale was used.[66,67]

Objectives and Research questions of this thesis

Although all NMDs ultimately result in muscle weakness, the pathophysiology is completely different in SMA and DMD. In SMA, the neuronal input to the muscle is impaired because of the motor neuron disease, whereas in DMD the muscle itself is affected. It is conceivable that the mandibular function is impaired differently in SMA and DMD. The overall objectives of this thesis are therefore (1) to characterize the impairments of the mandibular function in patients with SMA and DMD compared to healthy subjects, (2) to assess possible differences in pathophysiology and clinical presentation of compromised mastication in SMA and DMD patients and (3) to investigate whether specific training programs can help to cope with the impaired mastication and improve or stabilize detoriation of the mandibular function in DMD.

The general research questions of this thesis are:

PART I: Spinal muscular atrophy

1 What is the prevalence of impaired mandibular function in SMA?

2 Is the bulbar muscle function affected by SMA type 2 and 3?

3 What is the underlying mechanism for the impairment of mandibular function in SMA?

PART II: Duchenne muscular dystrophy

4 What is the prevalence of impaired mandibular function in DMD?

5 What are predictive factors for mandibular function in DMD?

6 What is the underlying mechanism for the impairment of mandibular function in DMD?

7 What is the efficacy of training the masticatory muscles using chewing gum in DMD?

PART III: Comparison, integration and implementation

I. What are the similarities between SMA and DMD?
II. Are there differences between SMA and DMD in clinical presentation and underlying mechanisms in the masticatory system?
III. Is there a need for specific training advice for SMA and DMD?
IV. Which disease-specific recommendations for training protocols can be given in SMA and DMD?

Outline of the thesis

After the general introduction (chapter 1), the research questions have been addressed in the following chapters. Chapter 2 describes a pilot study on the impairment of mandibular function in SMA type 2. Chapter 3 describes the mandibular movements, bite force and masticatory performance of patients with SMA type 2 and 3 and the predictive factors for mandibular dysfunction in these patients. In chapter 4, a cross-sectional study of MMO in 145 patients with SMA types 1-4 and 119 healthy controls is described. By performing magnetic resonance imaging (MRI) in 12 patients the masticatory muscles and mandibular condylar shape and sliding are visualized. Associations of a reduced MMO with SMA severity and complaints of dysphagia are analysed. Chapter 5 describes whether the masticatory performance and bite force in patients with DMD is different from these parameters in healthy individuals. The predictive factors for the masticatory performance in DMD are analyzed. In Chapter 6 the mandibular movements in patients with DMD are described and compared to those in healthy individuals. The predictive factors for the maximum mouth opening in DMD are analyzed. Chapter 7 describes the investigation of the efficacy of mastication in DMD by using a structured exercise program with chewing gum. In Chapter 8 the findings of the studies described in the previous chapters are discussed. Some recommendations for further research in this field are also provided. Chapter 9 summarizes the studies of the thesis, in the English and Dutch language respectively.

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PART I

Spinal muscular atrophy

Chapter 2

Impaired mandibular function in spinal muscular atrophy type 2: need for early recognition

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Abstract

Objectives: The aim of the study is to assess mandibular function in young patients with spinal muscular atrophy (SMA) type 2.

Methods: Twelve children and young adults with SMA type 2 and 12 healthy gender and age matched controls participated.

Results: The mandibular function impairment was moderate to severe in 50% of patients. A limited active maximum mouth opening (aMMO ≤ 30 mm) was observed in 75% of the patients. In patients with a severe reduction of the mandibular range of motion the temporomandibular joint mainly rotated during mouth opening instead of the usual combination of rotation and sliding. The severity of the limited aMMO correlated with the severity of the disease (Motor Function Measure scores).

Conclusions: This study shows that mandibular dysfunction is common among young patients with SMA type 2. Early recognition of mandibular dysfunction may help to prevent complications such as aspiration as a result of chewing problems.

Introduction

Spinal muscular atrophy (SMA) is a severe neuromuscular disorder characterized by degeneration of α motor neurons in the spinal cord, causing weakness and muscular atrophy.[1] With an incidence of about 1: 6000 to 10.000 it is one of the most common autosomal recessive diseases and an important hereditary cause of childhood morbidity.[2,3] SMA is caused by the homozygous deletion of the survival motor neuron (SMN) 1 gene that has been mapped to chromosome 5q11.2–13.3.[4] SMA severity varies considerably, and age at onset and the extent of motor impairment are used to distinguish 4 subgroups. [5-9]

Problems with biting and chewing are often reported by patients with SMA but there are few studies that have systemically addressed this issue. These studies mentioned feeding-related problems, weaker bite force of the masticatory muscles, reduced mandibular range of motion (ROM), abnormal craniofacial growth patterns and dental malocclusions which might cause chewing difficulties in children and young adults with SMA type 2 .[10-13] Rehabilitation and modern management of complications have improved the quality of life and life expectancy of children with SMA.[14] Management of non-fatal complications of the disease, such as strong limitations in the mandibular function that compromise feeding, chewing, oral hygiene and dental care becomes increasingly important. The mechanisms that cause mandibular dysfunction are not well known. Dysfunction of the temporomandibular joint, weakness of the masticatory muscles (mouth openers and closers) and reduced head balance may all be involved. Management of the mandibular dysfunction depends on insight in these mechanisms. The aim of the present study was to systemically investigate mandibular function by a combination of questionnaires and comprehensive clinical examination in young patients with SMA type 2.

Methods

A cross-sectional study was performed from June 2008 to June 2009. The studied population consisted of 12 patients with a genetically confirmed diagnosis of SMA type 2. Age limits were set from 5 to 19 years, to ensure patient cooperation. Patients with SMA type 2 were recruited in the Netherlands from the multidisciplinary outpatient clinic of the Children Hospital at the Radboud university medical center, department of Oral and Maxillofacial Surgery of the University Medical Centre Utrecht and from the multidisciplinary neuromuscular outpatient clinic of the Wilhelmina Children Hospital (Spieren voor spieren Centre for pediatric neuromuscular disorders), University Medical Centre Utrecht. All patients were wheelchair bound and had weakness of the neck muscles and scoliosis of the

spine. Ten patients had been treated surgically for scoliosis.

A group of 12 healthy children and young adults matched for age and gender acted as a control. They underwent the same clinical examination as the patients with SMA.

The study was approved by the Committee on Research Involving Human Subjects of Arnhem, Nijmegen and Utrecht, the Netherlands, and informed consent of the parents and children was obtained.

Questionnaires

The patients completed 3 questionnaires. The first (Screen) was developed to assess pain characteristics in the head and neck region, and temporomandibular function.[15,16] The second questionnaire (Mandibular Function Impairment Questionnaire) consists of 17 questions which can be answered on a five-level Likert scale, to assess to what extent the patient has difficulties to perform particular mandibular functions such as chewing and yawning. The raw score of the scale (ranging from 0 to 1) can be converted to a qualitative level of impairment; no/low (I), moderate (II) and high (III).[17] Previous studies have considered the Mandibular Function Impairment Questionnaire to be a reliable and valid tool.[18] The third questionnaire (Patient Specific Approach) identifies complaints of mandibular function through the selection of the activities from a list of 27, which cause discomfort.[19]

Physical motor skills

Motor skills were assessed in 6 patients from the multidisciplinary outpatient clinic of the Children Hospital, Radboud university medical center, the Netherlands by using the Motor Function Measure (MFM), performed by one physiotherapist.[20] Items 13 to 23 of the MFM test were designed to collect information about posture, arm and neck function and head control.

Clinical examination

Patients in this study were clinically examined following the validated procedure as described by Lobbezoo-Scholte et al. (1993, 1994).[21,22] Clinical examination consisted of the following parts: history taking of the main complaints; the current and experienced limitations of mandibular function; the dental, medical and personal history of the patient; an extra-oral inspection of the head and neck; and an intra-oral inspection of the dentition and the soft tissues.

The mandibular function was assessed by examining the mandibular ROM, including

active maximum mouth opening (aMMO) measured at the mesioincisal angle of the upper and lower front teeth (Figure 2.1), left and right lateral movement and protrusion, and passive maximum mouth opening (pMMO). The overbite and overjet were measured (Figure 2.1).

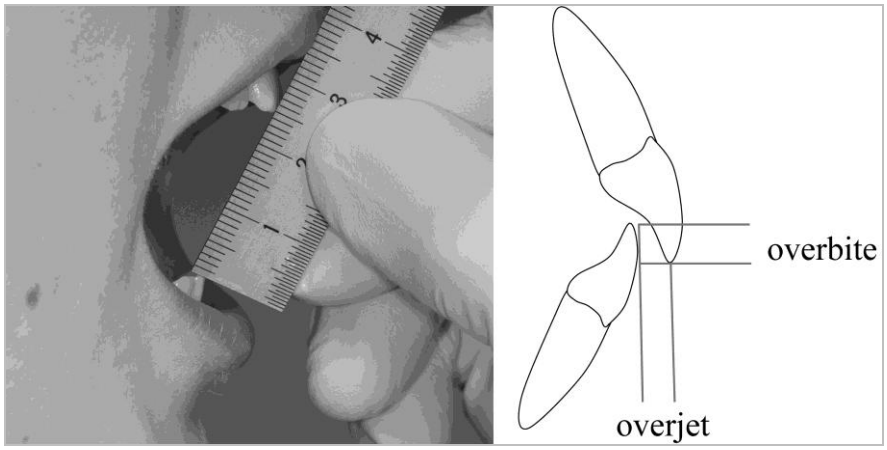

Figure 2.1. Measurement of the maximum voluntary mouth opening: the distance between the mesioincisal angle of the right upper and lower front teeth plus the overbite. Overbite refers to the vertical overlap of the front teeth and overjet to the horizontal overlap.

The patients' pain report during mandibular movements was recorded on a 5-point scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. The masticatory muscles (masseter, temporales, sternocleidomastoïd and occipital muscles) were palpated to assess painfulness. The temporomandibular joints were palpated on the left and right side with the mouth closed and open (lateral pole and posterior via the external acoustical meatus). Pain provocation and the extent of condylar movements were assessed. The mobility of the temporomandibular joint was assessed by traction and translation.

Statistical analysis

SPSS 15.0 was used to analyse the collected data. The correlation between MFM scores and level of aMMO was tested using the nonparametric Kendall rank correlation. The level of significance was set at $p = 0.05$.

Results

Patients with spinal muscular atrophy type II had a mean age of 11.8 years (range, 6 years and 4 months to 19 years); controls had a mean age of 12.3 years (range, 6 years and 4 months to 19 years and 3 months). Characteristics of the patients are summarized in Table 2.1.

Table 2.1. Characteristics of the spinal muscular atrophy type 2 group (n = 12) to investigate manbibular function

Patient number	Gender	Age (yrs. mths)	Age at diagnosis (mths)
1	F	6.5	21
2	M	7.2	12
3	M	7.8	12
4	F	8.9	prenatally
5	F	10.3	8
6	M	9.5	8
7	F	13.0	21
8	M	13.2	3
9	F	13.4	21
10	F	15.4	16
11	F	16.9	10
12	F	19.0	12

Abbreviations: M, male; F, female.

Questionnaires

Screen

One of the patients did not complete the questionnaires. The patients with SMA type 2 did not spontaneously report pain in rest or when using the masticatory system. Three patients did not have chewing difficulties and didn't report any limitation of mandibular function. Seven were aware of mouth opening limitations. They were not able to recall the time of onset of these limitations. They all experienced the limitations of mandibular function as a part of their disease.

Mandibular Function Impairment Questionnaire

Functional impairment, expressed as the raw score of the degree of masticatory and non-masticatory impairment, ranged from 0 to 0.6 (Table 2.2). Two patients had a severe

impairment, 3 had a moderate impairment, and 6 no/low impairment.

Patient Specific Approach

The main complaints of the 9 patients with limitation of mandibular function assessed through screen and the Mandibular Function Impairment Questionnaire were problems when chewing food, eating sticky and hard food and brushing the teeth.

Table 2.2. Mean values and standard deviations for the extent of functional impairment of patients with spinal muscular atrophy type 2 based on the total score in the Mandibular Function Impairment Questionnaire and active maximum mouth opening

Functional impairment[b]	N	MFIQ raw score[a]	aMMO[c] in mm (SD)
I	6	0.12	32.33 (13.19)
II	3	0.41	25.33 (4.51)
III	2	0.53	19.5 (0.71)

[a]MFIQ: seventeen questions with answers on a five-level Likert scale, to assess the extent of the difficulties experienced to perform a particular mandibular task. The total score of the scale (C) is the sum of the 17 items (S) divided by 4 times the number of items (n): C = S / 4n.

[b]Functional impairment is a conversion of the raw score: I= no/low, II= moderate, III= severe.

[c]aMMO: active maximal mouth opening, the maximum interincisal distance on opening as wide as possible.

Physical abilities

A total of 3 out of 6 patients from the department of Rehabilitation, Children's Hospital, Radboud university medical center, the Netherlands, had a low score on the MFM indicating problems with head balance. One out of 6 patients could keep head balance but had to compensate during item 14 of the MFM; Two out of 6 patients had no difficulty keeping head balance (Table 2.3).

Table 2.3. Active maximal mouth opening and Motor Function Measure in patients with spinal muscular atrophy type 2 (n = 6).

Patient number	Gender	Age yrs. mths	aMMO[a]	MFIQ, raw score[b]	MFM total[c] %	MFM 13[d]	MFM 14[e]
6	M	9.5	19	0.60	43	0	1
2	M	7.2	19	0.25	39	3	2
5	F	10.3	20	0.46	64	0	1
9	F	13.4	29	0.22	94	3	3
1	F	6.5	38	0	93	3	3
7	F	13.0	44	0	91	3	3

[a]aMMO: active maximal mouth opening, the maximum interincisal distance on mouth opening as wide as possible.

[b] MFM = Motor Function Measure, MFM score / percentage of maximal score of the items 13 to 23 (total score 33 points = 100%); MFM scoring per item: 0 = does not initiate movement or starting position cannot be maintained; 1 = partially completes the exercise; 2 = completes the exercise with compensations, slowness or obvious clumsiness; 3 = completes the exercise with a standard pattern.

[c] MFM score item 13: Seated on the chair. Without support of upper limbs or leaning against the back of the chair, maintains the sitting position, head and trunk in the axis; score 0 – 3.

[d] MFM score item14: Seated on the chair or in their wheelchair. Head in flexion: from the fully flexed position, raises the head and maintains the raised position, head in the axis during the movement and when maintained; score 0 – 3.

Examination of the masticatory system

Ranges of motion during active mandibular movements and passive maximum mouth opening (pMMO) were significant less in the patient group than in the control group (Table 2.4).

In patients with a severe reduced mandibular ROM (≤ 30 mm) the temporomandibular joints mainly rotated in aMMO, instead of the usual combination of rotation and sliding of the mandibular condyle. Mild pain could be provoked in 2 out of 12 patients during traction and translation, compression and resistance tests. Mild pain was reported in the masseter muscle region in 8 out of 12 patients during pMMO. In the control group none of the patients reported pain during clinical examination.

The severity of the limited aMMO correlated with the severity of the disease assessed by the MFM total scores (Table 2.3, $p \leq 0.05$).

Table 2.4. Group comparison and descriptive statistics of the mandibular range of motion of the mandible during clinical examination in the patient group (n=12) and in the control group (n=12)

Clinical examination	Patient group Mandibular ROM (mm)			Control group Mandibular ROM (mm)			p-value [a]
	Mean	SD	range	Mean	SD	range	
aMMO[b]	27.6	10.5	16 – 48	54.7	6.4	44 – 66	<0.001*
pMMO	28.7	10.7	16 – 49	56.8	6.6	44 – 65	<0.001*
Lateral movement right	4.1	3.7	0 – 9	9.8	2.8	5 – 13	<0.001*
Lateral movement left	4.1	4.0	0 – 11	9.8	2.2	6 – 12	<0.001*
Protrusion	1.3	1.6	0 – 5	7.9	2.7	4 – 13	<0.001*
Overbite[d]	1.8	3.7	-7 – 5	3.0	1.5	1 – 6	0.288
Overjet[e]	6.0	3.2	3 – 14	3.1	2.0	1 – 7	0.014*

[a]p-value, significant difference (*) between the patient group and the control group ($p \leq 0.05$).

[b]aMMO: active maximal mouth opening, the maximum interincisal distance on opening as wide as possible.

[c]pMMO: passive maximum mouth opening, the maximum interincisal distance on active opening, with a slight overpressure on the edges of the upper and lower front teeth by the examiner plus the vertical overbite.

[d]Overbite and [e]Overjet: see Figure 2.1.

Discussion

The aim of our study was to systematically investigate mandibular function by using questionnaires and detailed clinical examination in young patients with SMA type 2. We found a striking difference in the mandibular ROM between the patient group and control group, both statistically significant and clinically relevant.

Four out of 9 children with a severe limitation of aMMO (≤ 30 mm) scored a low function impairment on the MFIQ (Table 2.2) which indicates a discrepancy between these limitations and the awareness of the patients and parents. This lack of awareness may result in

limitations of mandibular function that are more extensive than if they were observed earlier. In the 9 patients with a severe reduced aMMO (≤ 30 mm), the stiff end feel in assisted mouth opening and mainly rotation of the mandibular condyles in pMMO indicates changes in the morphology of the temporomandibular joints. These changes might be initiated by inadequate movement of the lower jaw caused by the progressive weakening of the chewing muscles and the neck muscles leading to contracture of the temporomandibular joints. Some of our patients had a limited aMMO at a very young age, i.e. 7 years old. It is therefore important to investigate whether early physiotherapy, starting when mandibular movements are still within the normal range, might be more efficacious than late intervention. This requires early recognition of the reduced mouth opening. Physicians may not be aware of mandibular dysfunction as a complication of SMA, despite the fact that it may reduce the quality of chewing of solid food and compromise swallowing. A recent study showed that swallowing of solid food by patients with SMA type 2 resulted in more post-swallow residue especially in the vallecula and above the upper esophageal sphincter than with liquid.[23] Hampered chewing due to malocclusion, reduced bite force, and fatigue caused by the involvement of the chewing muscles (central nerve V_3, VII, IX and XII), results in a hampered food comminution, inadequate food bolus formation and oral transport. Thus, the already impaired swallowing process may be further hampered by the compromised chewing capability. Impaired chewing may be a clinically relevant impairment in children with SMA type 2. Moreover, the limited mandibular ROM has an impact on the oral hygiene and dental care.

Weakness of neck muscles may further contribute to impaired mandibular function. Head retraction by the neck muscle in an attempt to stabilize the balance of the head may increase reduction of the opening capacity of the mouth.[23] This is supported by the finding that MFM scores, which reflect motor disability in patients with neuromuscular disorders, were associated with mandibular dysfunction (Table 2.3, $p \leq 0.05$).[20]

Limitations of aMMO can be easily assessed by means of a ruler. Interincisal distances (including the overbite; Figure 2.1) of ≤ 35 mm in children younger than 12 years of age, and ≤ 40 mm in children older than 12 years suggest limited aMMO and warrants referral to a specialized dental team.

More research is needed to further assess the causative factors of a reduced mandibular function and to establish the additional value of an early physiotherapeutic intervention.

Conclusion

This study shows that mandibular dysfunction is common among young patients with SMAtype 2. This may reduce the quality of chewing and swallowing. Early recognition of mandibular dysfunction may help to prevent complications such as aspiration as a result of chewing problems.

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Chapter 3

Bulbar muscle dysfunction in patients with SMA type 2 and 3

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van Bruggen HW, Wadman RI, Bronkhorst EM, Meeuw M, Creugers NHJ, Kalaykova SI, Steenks MH. Bulbar muscle dysfunction in patients with SMA type 2 and 3.

Abstract

Objectives: Problems with feeding and swallowing are often reported by patients with hereditary proximal spinal muscular atrophy (SMA) but have not been studied objectively. We aimed to determine: 1) the impact of SMA type 2 and 3 on the mandibular function reflected as masticatory performance, mandibular range of motion, and bite force; 2) the predictors of mandibular dysfunction.

Methods: Sixty patients with SMA type 2 and 3 (mean age 16.7±7.7 years) and 60 age-matched controls filled out questionnaires about the impairments of the mandibular function. All participants underwent detailed clinical examination to document the mandibular range of motion including maximal mouth opening, bite force and masticatory function.

Results: All mandibular movements including mouth opening, lateral range of motion and protrusion of the mandible, were reduced in patients with SMA type 2 and 3 compared to healthy controls ($p < 0.001$). Maximal bite force was 19% lower in patients than controls, and more in patients with SMA type 2 than type 3. The strongest predictive factor was SMA type for impairment of mandibular range of motion ($R^2 = 0.82$) and weakness of neck muscles for bite force ($R^2 = 0.47$).

Conclusions: Reduced mandibular mobility and bite force are common complications in SMA. SMA type and neck muscle strength are important correlates of these complications. We provide further evidence for clinically relevant bulbar involvement in patients with SMA.

Introduction

Hereditary proximal spinal muscular atrophy (SMA) is caused by the homozygous deletion of the survival motor neuron (SMN) 1 gene and is characterized by degeneration of the alpha motor neurons in the spinal cord.[1] Weakness is most prominent in axial and proximal muscle groups but also affects bulbar muscles.[2, 3] There is large variation in SMA severity, and age at onset and highest achieved motor milestones are used to distinguish 4 types in descending order of severity.[4, 5] Natural history studies have shown that weakness is slowly progressive.[5] The function of bulbar muscle groups in patients with SMA has not been studied extensively, despite the fact that bulbar dysfunction may complicate chewing and swallowing, and may increase the risk of airway tract infections, weight problems and insufficient oral hygiene.[6, 7, 8] The most common complaints in questionnaire based studies were chewing difficulties (28%), perceived limitations in the ability to open the mouth (30%) and swallowing difficulties (25%) in a cohort of patients with SMA type 2; difficulty bringing food to the mouth (20%), difficulty chewing (20%) and choking (31%) in a sample of patients with SMA type 2 and 3.[6, 9, 10]

The oral phase of the swallowing process requires the concerted action of the tongue and muscle groups involved in mouth opening and mastication. Reduced mandibular range of motion and weakness of masticatory and tongue muscles complicate eating and swallowing in patients with SMA,[7, 12] but the function of these muscle groups has only been studied in small patient groups.[11] In this study we therefore investigated the prevalence and determinants of reduced mandibular range of motion, bite force and masticatory performance in a cohort of 60 patients with SMA types 2 and 3.

Methods

Participants

We performed a cross-sectional study between October 2013 and July 2014. We invited 93 patients with SMA types 2 and 3 aged 5 years or older listed in the Dutch SMA registry to participate in this study. All patients had a genetically confirmed diagnosis of SMA. We used diagnostic criteria of the SMA Consortium to define SMA types 2 and 3.[14-16] In short; SMA type 2 was defined as an onset between the ages of 6 and 18 months and having learned to sit but not to walk independently. SMA type 3 was defined as an onset after the age of 18 months and having learned to walk independently at some stage in life. Patients with type 3 and an onset before 3 years were classified as type 3a whereas an onset after the age of 3 was

classified as type 3b.[7] The presence of homozygous SMN1 deletion was confirmed in all patients using Multiplex Ligation-dependent Probe Amplification (MLPA) (SALSA MLPA kit P060 version B2, (www.mlpa.com; www.mrcholland.com). 64 patients gave informed consent; 4 participants were excluded from final analysis because of their medical history (osteotomy of the mandible) and temporomandibular joint disorder (TMD). Patient characteristics are summarized in Table 3.1.

We enrolled 60 age and gender-matched healthy controls. The control group was recruited at a primary and a secondary school located in the western part of the Netherlands, and consisted of children and parents. Controls aged 18 years and older were additionally recruited at the College of Dental Sciences, Nijmegen, The Netherlands. Inclusion criteria for healthy controls were the absence of a history of neuromuscular disease, temporomandibular disorders, ongoing orthodontic treatment or the presence of morphologic dental malocclusions (i.e. cross bite or tendency to cross bite).

This study was registered at the Central Committee on Research involving Human Subjects, the Dutch registry for clinical trials. The Medical Ethical Committee of the University Medical Center Utrecht approved the research protocol. Written informed consent was obtained from all participants and the legal guardians of the under aged participants.

Protocol

All patients and controls were examined at their homes or in the dental office by one of the authors who is a dental specialist (H.W.v.B.). The participants in both the patient and the control group completed structured questionnaires and were interviewed to document their medical history and difficulties with feeding and swallowing. A feeding disorder was defined as selectivity or avoidance of food or mastication. A swallowing disorder or dysphagia was defined as a disorder in one or more phases of the swallowing process; the oral, the pharyngeal or esophageal phase, i.e. problems to move food or fluids from the oral cavity to the throat or delayed passage of food or drink through the esophagus. Choking was defined as frequent blockage of the throat by food or drinks. The participants underwent a systematic clinical examination of the masticatory system, including anterior maximum voluntary bite force (MVBF) and masticatory performance measurements. Motor abilities were documented during the intake by one of the authors (R.I.W.) using the Hammersmith Functional Motor Scale Expanded (HFMSE) and muscle strength of neck flexors and extensors with the 5-point Medical Research Council (MRC) scale. [19, 20]

Questionnaires

The patient group and the control group completed two questionnaires: 'Screen' and the 'Mandibular Functional Impairment Questionnaire' (MFIQ).[21-23] Screen was developed to assess pain in the head and neck region, mandibular function and related issues and general health factors (e.g. medication, family history). Participant's ≥ 10 years of age reported pain on a Visual Analogue Scale (VAS, 0-100 mm) and children < 10 years on a 5-point Likert smiley pain scale which was converted to a VAS score.

MFIQ measures impairments of the function of the masticatory system reliably.[24] MFIQ consists of 17 questions, which can be subdivided into two dimensions - functional capacity and feeding - and is rated on a 5-point Likert scale ranging from '0' (no difficulty) to '4' (very difficult or impossible without help). The ratings are added to give a sum score (S, range 0–68). A higher score indicates more perceived mandibular function impairments and a MFIQ score of '0' indicates no impairment in mandibular functioning.

Clinical examination

We examined all participants following a validated procedure as described by Lobbezoo-Scholte and co-writers.[25, 26] All participants were in the upright position with their heads in a neutral position, non-ambulant patients with SMA were in their wheel chairs with their heads as far as possible in neutral position.

We assessed mandibular movements, including active maximum mouth opening (aMMO), left and right lateral ROM and protrusion, overbite and overjet with a metal ruler (mm) (Figure 3.1 A, B).[9] The aMMO was the distance measured between the incisal edges of the upper and lower right central incisors plus the overbite.

The masseter and temporalis muscles were palpated and both condyles in an open and closed mouth position to quantify pain felt by the patient (Figure 3.1 C). We assessed the mobility of the temporomandibular joint during aMMO by palpation of the lateral pole of the mandibular condyle with the index finger.[27]

We documented the number of occlusal contacts (OC-score) between the premolar and molar teeth of the upper and lower jaw after using wax records (Moyco beauty pink plate wax, 2270 g). A perforation in the wax record indicated an occlusal contact. Unilaterally, the maximum OC-score is 5 (1 OC per posterior occluding pair); bilaterally the maximum is 10.

Dental occlusion, defined as the static contact between the masticating surfaces of the maxillary and mandibular teeth in a closed position, was assessed regarding the presence or

absence of uni- or bilateral abnormal transverse relationship of single or multiple posterior teeth (i.e. premolars or molars) (Figure 3.1 D, E).

Measurement of the anterior maximum voluntary bite force

To measure the bite force we used the VU University Bite Force Gauge (VU-BFG) (Figure 3.1 F).[28] This is a handheld device that uses a load cell (LPM 510 250lb) to measure maximum voluntary bite force (MVBF) in kg, ranging from 0 to 50 kg in a linear fashion. The bite force transducer was calibrated before, half way and at the end of the data collection. Patients and healthy subjects clenched, with the strain gauge between the incisors, as hard as possible for 3 seconds and repeated clenching three times with an interval of 30 seconds rest periods; the highest value of the three measurements was used.

Masticatory performance: mixing ability test

We defined masticatory performance as an individual's capacity to grind or pulverize a test food after a fixed number of chewing cycles. For this purpose, we used the mixing ability test (Figure 3.1 G, H).[29] Each participant performed 20 chewing strokes on a wax tablet (at room temperature, 20 °C) consisting of a red and a blue layer. As a result the colours would mix and the degree of mixing represented the masticatory performance.

Statistical analysis

IBM SPSS version 20 was used for statistical analysis. The level of significance was set at $p = 0.05$. Descriptive statistics in terms of mean and standard deviation were used to describe the independent scale variables in the patient and control group. Paired Student's t-test was used to compare between-group continuous variable outcomes, and for dichotomous variables the chi-square test was used. To compare test outcomes between SMA type 2 and 3 ANOVA or Kruskal-Wallis test was used for scale variables and chi-square test for dichotomous variables.

To study the association between mandibular function variables and predictive factors, univariate linear regression analyses were performed. To identify contributing factors to reduced aMMO, the variables age, SMA type, disease duration, HFMSE, MRC sum score, MFIQ raw score, mixing ability, number of occlusal contacts, scoliosis surgery, mastication difficulties, dysphagia, difficulties biting of food and food adaptation were used. To identify determinants of reduced anterior MVBF, the variables age, SMA type, disease duration,

HFMSE, MRC sum score, MFIQ raw score, aMMO, number of occlusal contacts, scoliosis surgery, dysphagia, difficulties biting of food and food adaptation were used. The independent variables, which were possibly associated with the aMMO and the anterior MVBF ($p < 0.1$) were included in the multiple linear regression analyses (stepwise backward method; p-value to remove > 0.05) in order to determine the set of variables that best predict impaired aMMO and anterior MVBF in SMA patients.

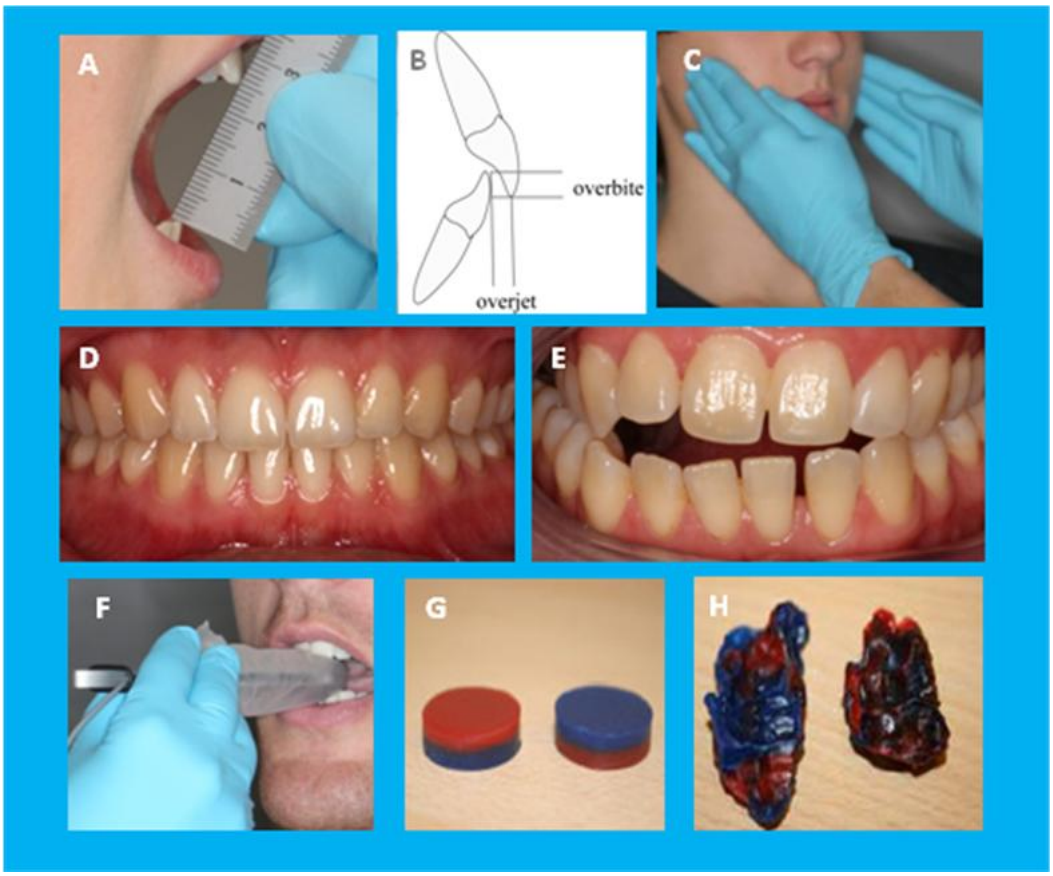

Figure 3.1. Main parameters to determine the bulbar involvement of the oral phase of swallowing in patients with SMA and the dentition of participants. (A) Measurement of the maximum voluntary mouth opening: the distance between the mesioincisal angle of the right upper and lower front teeth plus the overbite; B) overbite refers to the vertical overlap of the front teeth and overjet to the horizontal overlap; (C) palpation of the masseter muscle; (D) mandible in intercuspal position of a healthy subject; (E) dentition in intercuspal position of patient with SMA type 2 with cross bite on the right hand side and tendency to crossbite on the left side; (F) measurement of the anterior bite force; (G) a wax tablet ;(H) a chewed wax tablet of the mixing ability test.[24]

Results

Questionnaires

Screen and anamnestic information

19 patients (32 %) reported limitations in the ability to open the mouth (Table 3.2). The maximum intensity of the recorded pain in these 3 patients was 'mild'.

17 patients (28%) mentioned mastication difficulties. In 8 out of 17 patients (47%), mastication problems interfered with daily and social activities ranging from sometimes to very often. Dysphagia was reported by 28 patients (47%), more often in SMA type 2 than type 3a and 3b (Table 3.2). The controls did not report mastication problems or dysphagia.

Mandibular Function Impairment Questionnaire

Information on food adaptation by the patients, derived from the MFIQ, showed that 32 patients (54%) had to adapt food composition and consistency (Table 3.2). The controls did not report impairment of the mandibular function.

Clinical examination

Range of motion

aMMO, active lateral ROM and protrusion were significantly smaller in the patient group than in the control group (Table 3.1). Patients with type 2 had significantly smaller aMMO than type 3a and 3b (Table 3.2). The mean aMMO was smaller or equal than 40 mm in 50% of the patients with SMA. The mean active lateral ROM was smaller than 8 mm in 48% of the patients; in type 2 the active lateral ROM was significantly smaller than type 3a and 3b (Table 3.2). The active protrusion was smaller than 5 mm in 32% of the patients; in the SMA type 2 cohort protrusion was significantly smaller than in SMA type 3 (Table 3.2).

Active lateral ROM smaller than 5 mm was found in 3 controls (5%).

TMJ mobility

Clinical examination of the temporomandibular joint mobility showed that 45 patients (75%) had a normal sliding of the mandibular condyle with a mean aMMO of 45.2 mm (range 14 – 71 mm); 15 patients (25%) had a reduced sliding or no sliding with a mean aMMO of 17.1 mm (range 4 – 33 mm) (Table 2). All controls had normal sliding of the mandibular condyle with a mean aMMO of 54.8 mm (range 46 – 70 mm).

Pain

In two patients with SMA type 2, pain could be provoked during aMMO and during palpation of the masseter muscle (VAS 10/100 mm, 65/100 respectively).

Dental occlusion

The OC score in the posterior teeth of the upper and lower jaws was reduced in 14 % of the patients (average OC score 6.6, SD 2.2, range 1–10) compared with the controls (average OC score 7.7, SD 1.2, range 5–10) (Table 3.1). Twenty one patients (35%) showed tendency to cross bite; lateral cross bite was present in 17 (28%) patients (Table 3.2).

Maximum voluntary bite force

The MVBF was 19.0% lower in the patient group than in the control group (Table 3.1). Mean MVBF was 154.9 N (SD 85.3, range 18.6–374.6 N) in the patient group and 191.2 N (SD 86.3, range 67.7–490.3 N) in the control group. Patients with type 2 had a significantly lower MVBF than patients with SMA type 3 (Table 3.2).

Table 3.1. Group comparison and descriptive statistics of the mandibular range of motion, occlusal contacts, anterior maximum voluntary bite force (MVBF) in Newton and mixing ability during clinical examination in the patient group (n = 60) and in the control group (n = 60). Mean and standard deviation of the measurements are referred to as $\bar{x}$ (SD).

Clinical examination	Patient group	Control group	p-value
Age	32.3 (17.4)	31.1 (17.6)	0.397
range	8.7 – 70.3	8.2 – 70.9	
aMMO[a] (mm) (SD)	38.9 (15.3)	54.8 (5.4)	<0.001*
range	4.0 – 71.0	45.0 – 68.0	
Lateral ROM L/R[b] (mm) (SD)	8.0 (4.5)	10.4 (2.4)	<0.001*
range	0.0 – 19.0	5.0 – 15.5	
Protrusion[c] (mm) (SD)	6.5 (4.0)	9.6 (2.1)	<0.001*
range	0.0 – 14.0	5.0 –15.0	
Occlusal contacts[d]	6.6 (2.2)	7.7 (1.2)	0.001*
range	1.0 – 10.0	5.0 – 10.0	
Anterior MVBF[e]	154.9 (85.3)	191.2 (86.3)	0.018*
range	18.6 – 374.6	67.7 – 490.3	
Mixing ability[f]	18.6 (3.0)	18.1 (2.8)	0.222
range	14.3 – 25,2	13.0 – 24.6	

* = Statistically significant differences.

[a]aMMO: active maximum mouth opening, the maximum interincisal distance on opening as wide as possible plus the vertical overbite.

[b]Lateral ROM L/R: active mandibular lateral excursion, mean value between the left and right side.

[c]Protrusion: active forward movement of the mandible.

[d]Occlusal contacts: the number of occlusal contacts between the premolar and molar teeth of the upper and lower jaw after the teeth were brought into occlusion.

[e]Anterior MVBF: maximum vertical interocclusal bite forces between the central incisors of the upper and lower jaw.

[f]Mixing ability: individual's capacity to grind a two colored wax tablet during 20 strokes of chewing.

Mixing ability test

Masticatory performance was comparable in the patient (18.6, SD 3.0) and control group (18.1, SD 2.8) (Table 3.1) and between SMA types ($p > 0.1$) (Table 3.2).

Predictive factors for aMMO and bite force

Univariate linear regression analyses showed that most of the selected determinants were associated with aMMO except for age ($p = 0.138$) and disease duration ($p = 0.736$). Multiple linear regression analysis showed that SMA type, MFIQ, difficulties biting of food and food adaptation as the independent predictive factors for reduced aMMO ($R^2 = 0.80$, Table 3.3).

Univariate linear regression analyses showed that all the selected determinants were associated with reduced MVBF. Multiple linear regression analysis identified age, and MRC sum score as the independent predictive factors for a reduced MVBF ($R^2 = 0.47$, Table 3.4).

Table 3.2. Characteristics of patients with spinal muscular atrophy (n = 60) presented by stages. Mean and standard deviation of the measurements referred to as $\bar{x}$ (SD); number of patient as n / %.

	SMA stage				p-value		
	Total (n = 60)	Type 2 (1) (n = 31)	Type 3a (2) (n = 18)	Type 3b (3) (n=11)	1-2 2-3a	2-3 3a-3b	1-3 2-3b
Mean age, yrs.mths	32.3 (17.4)	26.2 (15.0)	35.7 (19.6)	43.8 (12.4)	0.115	0.402	0.009*
range	8.7 – 70.2	8.7 – 70.2	8.7 – 65.7	21.8 – 58.1			
Disease duration, mths	312.6 (193.4)	266.4 (176.8)	369.2 (225.3)	350.2 (163.6)	-	-	-
range	52.7 – 777.7	55.5 – 777.7	52.7 – 687,6	90.5 – 534.7			
HFMSE[a]	14.8 (19.3)	3.7 (5.0)	17.7 (18.1)	41.1 (20.0)	0.177	0.118	<0.008*
range	0 – 66	0 – 20	0 – 45	8 – 66			
MRC sum score, neck[b]	3.6 (1.0)	3.0 (0.7)	4.0 (0.8)	4.9 (0.2)	0.075	0.024*	0.001*
range	2 – 5	2 – 4.5	2.8 – 5	4.5 – 5			
MFIQ raw score[c]	0.14 (0.17)	0.20 (0.20)	0.10 (0.11)	0.03 (0.03)	0.341	0.459	0.012*
range	0.36 – 0.31	0.0 – 52.0	0.0 – 0.35	0.0 – 0.09			
aMMO	38.9 (15.3)	28.9 (12.5)	44.7 (8.2)	57.5 (7.4)	0.001*	0.090	<0.001*
range (mm)	4.0 – 71.0	4.0 – 53.0	23.0 – 54.0	48.0 – 71.0			
Lateral ROM L/R	8.0 (4.5)	5.8 (4.3)	8.8 (2.5)	12.5 (3.9)	0.058	0.190	<0.001*
Range (mm)	0.0 – 19.0	0.0 – 15.0	4.0 – 13.0	6.5 – 19.0			
Protrusion	6.5 (4.0)	4.6 (3.6)	7.9 (3.6	9.3 (3.5)	0.006*	0.595	0.001*
Range (mm)	0.0 – 14.0	0.0 – 13.0	0.0 – 14.0	5.0 – 14.0			
Anterior MVBF	154.9 (85.3)	118.7 (68.6)	177.5 (88.3)	218.7 (78.5)	0.031*	0.353	0.001*
range (N)	18.6 – 374.6	18.6 – 261.8	47.1 – 374.6	83.4 – 345.2			
Mixing ability	18.6 (3.0)	19.7 (3.3)	17.7 (2.2)	17.2 (1.4)	0.109	1.000	0.106
range	14.3 – 25,2	14.3 – 25.2	14.3 – 24.1	15.0 – 19.4			
Occlusal contacts	6.6 (2.2)	6.5 (2.1)	6.8 (1.9)	7.5 (0.8)	0.269	0.122	0.005*
range	1 – 10	2 – 10	1 – 8	6 – 8			
Ventilatory support					0.409		
None	47 / 78 %	22 / 74 %	14 / 78 %	11 / 100 %			
Part-time (nocturnal)	7 / 12 %	5 / 16 %	2 / 11 %	0 / 0 %			
Cont. noninvasive	3 / 5 %	3 /10 %	0 / 0%	0 / 0%			
Conti. + tracheostomy	3 / 5 %	1 / 3 %	2 / 10%	1 / 10%			
Scoliosis surgery	30 / 50%	23 / 74	7 / 39 %	0 / 0%	<0.001*		
Dysphagia[d]	28 /47 %	19 / 61 %	8 / 44 %	1 / 10%	0.010*		
aMMO reduced, subjective[e]	19 / 32 %	17 / 55 %	2 / 10 %	0 / 0 %	<0.001*		
Sliding of the TMJ[f]	15 / 25%	14 / 45 %	1 / 6 %	0 / 0%	0.001*		
Mastication difficulties[g]	17 / 28 %	12 / 39 %	4 / 22 %	1 / 10%	0.159		
Difficulties biting of food[h]	24 / 40 %	19 / 61 %	5 / 28%	0 / 0 %	<0.001*		
Food adaptation[i]	32 / 53 %	21 / 68 %	9 / 43%	2 / 18 %	0.017*		

* = Statistically significant differences.

SMA = spinal muscular atrophy; SMA type 2 = onset between the ages of 6 and 18 months and learned to sit or even shortly stand but not to walk independently; type 3a = onset after the age of 18 months but before 3 years and learned to walk independently at some stage in life; type 3b = onset after the age 3 years and learned to walk independently at some stage in life.

[a]HFMSE: the Hammersmith Functional Motor Scale Expanded contains 33 items with total scores ranging from 0 to 66. Each activity (item) is scored on a 3 point scoring system, with a score of 2 for unaided, 1 for assistance and 0 for inability. A total score can be achieved by summing the scores for all the individual items. The total score can range from 0, if all the activities are failed, to 66, if all the activities are achieved. All items have to be tested without spinal jacket or orthoses.

[b]MRC sum score = the sum score of the neck muscle strength evaluated by the Medical Research Counsil scale, a categorical scale to measure the entire range of muscle strength, from 0 (no visible or palpable muscle contraction) through 5 (movement through the complete range of motion against gravity and maximum resistance).

[c]MFIQ raw score: seventeen questions with answers on a five-point Likert scale, to assess the extent of the difficulties experienced to perform a particular mandibular task. The total score is the score of the degree of masticatory and non-masticatory impairment that represents the total function impairment. The total score of the scale (C) is the sum of the 17 items (S) divided by 4 times the number of items (n): $C = S / 4n$.

[d]Dysphagia: rated on a 5-point scale. 0 = never; 1 = sometimes; 2 = regularly; 3 = often; 4 = not applicable. Patients with a score >1 are considered to have difficulty in passing food or drinks from the mouth into the stomach expressed as choking solid food and, or sticking food in the throat.

[e]aMMO reduced, subjective: limitation in the ability to open the mouth noted by the patients in Screen or by anamnestic information.

[f]Sliding of the temporomandibular joint was assessed by palpation: reduced = no or hardly any sliding of the lateral pole of the mandibular condyle, normal = sliding to and beyond the crest of the articular eminence.

[g]Mastication difficulties: rated on a 5-point scale. 0 = never; 1 = sometimes; 2 = regularly; 3 = often; 4 = very often. Patients with a score >1 are considered to have mastication difficulties during mastication of hard, sticky or soft food.

[h]Difficulties with biting of food: rated on a 5-point scale. 0 = never; 1 = sometimes; 2 = regularly; 3 = often; 4 = very often. Patients with a score >1 are considered to have difficulties with biting of food.

[i]Food adaptation: patients unable to eat hard biscuits, meat, raw carrots, French loaf or nuts.

Table 3.3 Multiple linear regression analysis of predictors for the active maximal mouth opening (aMMO) in spinal muscular atrophy patients

Model	Effect	95 % Confidence Interval for Effect		p-value
		Lower Bound	Upper Bound	
(Constant)	38.98	34.955	43.006	<0.001*
SMA type				
type 2	Reference			
type 3a	9.87	5.396	14.333	<0.001*
type 3b	18.64	12.929	24.35	<0.001*
MFIQ	-39.21	-56.374	-22.047	<0.001*
Difficulties biting of food	-9.22	-14.778	-3.667	0.002*
Food adaptation	4.78	-0.202	9.768	0.060*

R^2 = 0.80; * = Statistically significant differences.

Table 3.4 Multiple linear regression analysis of predictors for anterior maximum voluntary bite force (MVBF) in spinal muscular atrophy patients

Model	Effect	95 % Confidence Interval for Effect		p-value
		Lower Bound	Upper Bound	
(Constant)	-45.95	-119.26	27.36	0.214
Age (in years)	1.38	.30	2.45	0.013*
MRC sum score	21.69	12.44	30.94	<0.001*

R^2 = 0.38; * = Statistically significant differences.

Discussion

Self-reported complaints of feeding, chewing, limitations in the ability to open the mouth, swallowing and choking range from 20-35% of patients with SMA type 2 and 3.[3,7,9] Patients in this study reported dysphagia (48%) more often than in previous studies, which may be due to the use of different definitions of dysphagia.[3, 6, 9] The frequency of mastication difficulties (28 %) was comparable with previous studies.[6, 9, 10] Self-reporting may not reflect true prevalence of mandibular functional problems.[6, 10] In our previous study, for example, we found a much higher than self-reported prevalence of limitations in mouth opening.[3] Moreover, although 28% of patients in our study reported mastication difficulties, more than half of the patients indicated that they adapted their food consistency. This underlines the importance of objectively measuring function of bulbar muscle groups.

Our data suggest that at least two important aspects of the mandibular function, i.e. ROM and bite force are diminished in patients with SMA types 2 and 3. SMA type, MFIQ, difficulties biting of food and food adaptation were identified as independent determinants of reduced mouth opening in our multiple linear regression model (Table 3.3). The model suggests that SMA type and questions about food handling are useful tools to identify patients with reduced aMMO. We previously showed that selective fatty degeneration of the lateral pterygoid muscle is associated with this complication, which explains the reduced sliding ability of the TMJ and the reduced lateral ROM.[3] As far as we know it is unclear at what value a lateral ROM may have a negative effect on masticatory performance. We assume that with a lateral ROM smaller than 3 mm the bolus formation is complicated.

The second finding is a reduced anterior MVBF, indicating weakness of masticatory muscles (i.e., the mandibular closing muscles). Decreased bite force in patients with SMA has been reported before and may be secondary to the fatty degeneration of the masseter and temporal muscles that we observed in a recent MRI-study of bulbar muscles.[6, 10] Multiple linear regression analysis in this study indicated that age and MRC sum score are determinants of reduced MVBF. This may reflect the natural history of SMA that is generally characterized by progression of muscle weakness with advancing age. Our data support a model for mandibular dysfunction caused by gradually increasing weakness of muscles that mediate mouth opening, closing and horizontal movements, leading to bite force reduction and development of progressive contractures of the TMJ.

It was surprising that masticatory performance did not differ between patients and control groups, since 28% of our patients reported masticatory difficulties. Moreover, self-reporting mastication difficulties may not reflect true prevalence due to the high percentage of

food adaptation in our patient group.[6, 10] The used methodology may lack sensitivity to identify masticatory problems for a number of reasons. First, masticatory performance as reflected by the wax tablet mixing test is primarily associated with the number of functional tooth units (OC score) and bite force in healthy subjects.[30] The mean OC score in the patient group was only one occlusal contact lower than in the control group. This, in combination with sufficient bite force, may explain the retained capacity to mix the wax tablets.

Masticatory performance was measured in the first 20 chewing cycles and therefore mimics the start of a meal. Fatigability, which may be an important additional problem to weakness in patients with SMA, may compromise masticatory function, but is obviously not covered by this test.[31] Future studies should preferably employ methodology designed to capture masticatory dysfunction in the course of a meal.

Recognizing bulbar involvement in SMA by medical staff, patients, parents and caretakers is a first step to identify risks of dysphagia, aspiration and insufficient intake. The use of MFIQ, a short questionnaire to assess mandibular functional problems, in combination with measuring aMMO may be helpful to identify patients with SMA who are at risk for bulbar problems. We also need to develop and test efficacy of specific training programs that aim at preserving mandibular function. These programs should include training of aMMO and horizontal movements, and possibly on the strength of masticatory muscles.

Conclusion

This study provides further evidence for clinically relevant bulbar involvement in patients with SMA type 2-3. Mandibular range of motion, and bite force were significantly lower in the patients compared to healthy controls. Reduced mandibular mobility and bite force are common complications in SMA with SMA type as the strongest predictor for mouth opening and strength of the neck muscles for the anterior MVBF.

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Chapter 4

Bulbar muscle MRI changes in patients with SMA with reduced mouth opening and dysphagia

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Abstract

Objectives: We performed a study in patients with proximal spinal muscular atrophy (SMA) to determine the prevalence of reduced active maximal mouth opening (aMMO) and its association with dysphagia as a reflection of bulbar dysfunction and visualized the underlying mechanisms using magnetic resonance imaging (MRI).

Methods: We performed a cross-sectional study of MMO in 145 patients with SMA types 1-4 and 119 healthy controls and used MRI in 12 patients to visualize mandibular condylar shape and sliding and the anatomy of muscle groups relevant for mouth opening and closing. We analyzed associations of reduced aMMO with SMA severity and complaints of dysphagia.

Results: Reduced MMO was defined as an interincisal distance ≤ 35 mm and was found in none of the healthy controls and in 100, 79, 50 and 7% of patients with SMA types 1, 2, 3a and 3b/4, respectively. MRI showed severe fatty degeneration of the lateral pterygoid muscles that mediate mouth opening by allowing mandibular condylar sliding but relatively mild involvement of the mouth closing muscles in patients with reduced aMMO. Reduced aMMO was associated with SMA type, age, muscle weakness and dysphagia ($p < 0.05$).

Conclusions: Reduced aMMO is common in SMA types 1-3a and is mainly caused by fatty degeneration of specific mouth opening muscles. Reduced aMMO is a sign of bulbar dysfunction in SMA.

Introduction

Hereditary proximal spinal muscular atrophy (SMA) is an important genetic cause of mortality in infants with early-onset SMA and leads to significant disability in children and adults with later onset of disease. SMA is caused by homozygous deletion of the survival motor neuron (SMN) 1 gene and is characterized by progressive predominantly proximal muscle weakness.[1] Degeneration of the alpha motor neurons in the spinal cord is the classic pathological hallmark of SMA. There is large variation in SMA severity, which is reflected by the distinction of SMA types 1-4.[2-6]

Involvement of the motor nuclei of the brainstem in SMA has been found in post-mortem studies and is suggested by the frequent finding of fasciculations in the tongue, dysphagia and several other often reported complaints by patients.[5, 7-12] Feeding problems were mentioned by more than a third of the patients with SMA type 2 in one survey and additional problems with mouth opening, biting and chewing that may further complicate eating have also been documented.[10, 11, 13-15] Dysphagia in SMA is probably caused by combined weakness of specific bulbar muscle groups and neck extensors.[13, 15] Limitations in mouth opening may represent a more straightforward model to study bulbar involvement in SMA.

We therefore investigated active maximal mouth opening (aMMO) in 145 patients with SMA types 1-4 and 119 healthy controls and visualized structural changes of bulbar muscle groups and temporomanibular joint (TMJ) morphology and dynamics in 12 patients with SMA types 2-4 with magnetic resonance imaging (MRI).

Methods

Patients and clinical assessment

We performed a cross-sectional study between July 2010 and July 2013 in 145 patients with a genetically confirmed diagnosis of SMA. All patients visited the outpatient clinic of the University Medical Center Utrecht. The presence of homozygous SMN1 deletion was confirmed in all patients using multiplex ligation-dependent Probe amplification (SALSA MLPA kit P060 version B2; MRC-Holland, Amsterdam, the Netherlands.

We documented medical history using National Institute of Neurlological Disorders and Stroke common data element Guidelines (www.commondataelements.ninds.nih.gov) and difficulties with eating, dysphagia or choking using a semi-structured systematic questionnaire from previous studies (appendix e-1 on the Neurology® web site at Neurology.org).[10, 11] We defined eating problems as frequent difficulties with biting,

swallowing and/or chewing. Dysphagia was defined as frequently occurring problems with swallowing, i.e. problems to move food or fluids from the oral cavity to the throat or delayed passage of food or drinks through the esophagus. We defined choking as frequent blockage of the throat by food or drinks.

We assessed aMMO by measuring the interincisal distance between the upper and lower front teeth at the mesioincisal angles with a ruler in all 145 patients and in 119 consecutive healthy controls recruited through Dutch primary and secondary schools and the College of Dental Sciences.[15] Two of the investigators (R.I.W. and H.W.v.B.) instructed and verbally stimulated participants to open their mouth as far as possible without pain.

We used age at onset and achieved motor milestones to define SMA types according to the diagnostic criteria defined by the SMA Consortium.[2-4] The definition of SMA type 1 was an onset before the age of 6 months and inability to sit independently. Patients with SMA type 2 had onset between the ages of 6 and 18 months and had learned to sit or even shortly stand, but not to walk independently. Patients with SMA type 3 developed weakness after the age of 18 months and had learned to walk independently at some stage in life. Patients with type 3 and an onset before 3 years were classified as 'type 3a' whereas an onset after the age of 3 was classified as 'type 3b'.[3] Finally, SMA type 4 was defined by an onset after the age of 30 in ambulatory patients.[3] In case there was a discrepancy between age at onset and achieved motor milestones, the latter was used to define SMA type.

One of the investigators (R.I.W.) assessed strength and motor function. We used the Medical Research Council (MRC) score to document muscle strength of neck flexors, neck extensors, deltoids, biceps, triceps, wrist flexors and extensors, finger flexors, extensors, and spreaders, illiopsoas, gluteus maximus and medius, hamstrings, quadriceps, adductors, tibialis anterior and plantar flexors of the feet in patients aged 5 years and older. The muscle sum score ranged between 34 and 170 (MRC 0 and MRC 1 were combined and given a score MRC 1). We used the Hammersmith Functional Motor Scale Expanded (HFMSE) to score motor function in all patients.[16, 17] The intra-rater test-retest variability showed a mean difference of 0.4 points (SD 2.7; SE 0.9; 95% CI -1.9–2.65).

Magnetic Resonance Imaging of the temporomandibular joint and associated muscles

MRI (Philips Achieva 3T, Sense Head 8-channel, Best, the Netherlands) of the TMJ, muscle groups involved in mouth opening (lateral pterygoid muscle, anterior belly of the digastric muscle, geniohyoid muscle) and mouth closing (masseter muscle, temporalis muscle, medial pterygoid muscle) and the neck extensors was performed in 12 adult patients with SMA type

2-4 and a 25-year old control subject. Patients were recruited from 47 eligible adults without exclusion criteria for MRI (i.e. signs of nocturnal hypoventilation, severe swallowing difficulties, > 15% forced vital capacity postural change between sitting and supine, presence of MRI incompatible spinal rod fixation material) who were asked by letter wether they were interested to participate.

T1-weighted and T2-weighted images with a slice thickness of 3 mm were generated in the transverse and (oblique) sagittal planes. TMJ anatomy and dynamics, e.g. condylar shape and sliding of the mandibular condyle relative to the articular tubercle, were investigated in oblique sagittal images perpendicular to the long axis of the condyles for each joint in closed- and open mouth positions. The latter position was maintained by means of a perspex bite block between the incisors.

A radiologist (T.D.W.) and a dental specialist (M.H.S.) who were blinded for patient characteristics independently scored the images (Cohen's kappa between investigators = 0.8). Disagreement between scores was resolved by reaching consensus. Fatty muscle degeneration was graded on a four-point-scale (1 = normal; 2 = mild atrophy or fatty infiltration; 3 = severe atrophy or fatty infiltration; 4 = complete atrophy or fatty infiltration).[18] Condylar shape and condylar sliding were scored as normal or abnormal. Condylar sliding was assessed as abnormal when in the open mouth position the mandibular condyle did not protrude to or beyond the crest of the articular eminence.

Standard protocol approvals, registrations, and patient consents

The Medical Ethical Committee of the University Medical Center Utrecht approved the research protocol. All patients and parents of patients younger than 18 years gave informed consent prior to inclusion. This study was registered at the Central Committee on Research involving Human Subjects, the Dutch registry for clinical trials.

Statistics

We tested normality with the Kolmorogov-Smirnov and Shapiro-Wilk Test. Disease duration and the age at inclusion had a very high correlation ($R^2 = 0.94$). Therefore, multivariate analyses were checked and corrected for colinearity. P values of < 0.05 were considered significant. Correlations were analyzed using Spearman's rho. Comparisons of clinical characteristics (e.g. age, disease duration, MRC sum score, HFMSE, aMMO, presence of dysphagia) between SMA types were performed using Kruskal-Wallis or Mann-Whitney U test (continuous data) or Chi-square/Fisher Exact analysis (dichotomous data). Univariate and

multivariate tests including dichotomous data were performed using (binary or multinominal) logistic regression. Multivariate linear regression analyses were performed with items that showed significant associations in univariate linear regression analysis. Receiver-operating characteristics (ROC) curves were generated to analyze the predictive value of clinical motor scores and aMMO for the presence of dysphagia. We used SPSS (IBM SPSS Statistics version 19, Chicago, IL) for statistical analysis.

Results

Patient characteristics

Patient characteristics are summarized in Table 4.1. Thirty-five percent of patients reported dysphagia or choking (Table 4.1). The majority of patients reported that they tried to prevent dysphagia and choking by changing the consistency of their food or posture during mealtimes.[12, 14] Sixteen patients (14%) out 115 patients with SMA types 1-3a had a history of recurrent choking. Six (4%) patients (3 type 1, 1 type 2, 1 type 3a and 1 type 3b) used a nasal-gastro- feeding tube and 13 patients (9%) with SMA types 1 and 2 had a percutaneous endoscopic gastrostomy.

Active maximum mouth opening

All healthy controls had aMMO of > 35 mm and reduced aMMO was therefore defined as ≤ 35 mm. aMMO was reduced in 57% of all patients and 100%, 79%, 50% and 7% of patients with SMA types 1, 2, 3a and 3b/4 respectively (Table 4.1). aMMO differed between SMA types ($p < 0.01$). These differences between SMA types were apparent from an early age on (Figure 4.1). aMMO declined with age and disease duration in patients with SMA type 1 and 2 (age: correlation coefficient -0.25, $p = 0.02$; disease duration: correlation coefficient -0.28, $p = 0.01$) (Figure 4.1).

Table 4.1. Patient characteristics

	All (n=144)	Type 1[a] (n=11)	Type 2 (n=76)	Type 3a (n=28)	Type 3b (n=27)	Type 4 (n=3)
Gender (F:M)	81:64	6:5	46:30	15:13	12:15	2:1
Mean age at inclusion, yrs	25.3	20	18.4	30.5	38.8	48.0
(range)	(1.8 – 78)	(4.1 – 48.9)	(1.8 – 65.7)	(2.3 – 64.7)	(14 – 78)	(41.3 – 52.5)
Mean age at onset, mths	39.6	4.9	11.3	19.8	114.9	444
(range)	(1 – 510)	(1 – 8)	(3.5 – 30)	(6 – 54)	(42 – 294)	(366 – 510)
Mean disease duration, yrs	21.8	20.5	17.2	28.8	32.2	10.9
(range)	(0.7 – 64.8)	(3.8 – 8.4)	(0.7 – 64.8)	(1.2 – 62.2)	(1.1 – 71.4)	(7.5 – 14.5)
Mean MRC sum score	101	58	87	108	142	156
(range)	(34 – 167)	(34 – 82)	(39 – 140)	(54 – 160)	(87 – 167)	(147 – 162)
Mean HFMSE score	15	0	8	20	34	48
(range)	(0 – 66)	(0 – 1)	(0 – 40)	(0 – 49)	(2 – 66)	(43 – 53)
aMMO, mm	31.4	10.5	26.7	35.6	46.6	50
(range)	(3 – 60)	(3 – 20)	(4 – 55)	(15 – 50)	(20 – 60)	(50)
Reduced aMMO, n (%)	83 (57)	12 (100)	55 (79)	14 (50)	2 (7)	0 (0)
Tongue fasciculations, n (%)	81 (60)	10 (100)	54 (76)	10 (37)	5 (20)	2 (67)
Eating problems, n (%)	65 (45)	7 (64)	15 (21)	4 (17)	1 (4)	0 (0)
Dysphagia, n (%)	46 (32)	7 (64)	27 (36)	11 (39)	1 (4)	0 (0)
Choking, n (%)	16 (11)	6 (55)	9 (12)	1 (4)	0	0 (0)

Legend: F=female; M=male; MRC= medical research counsil; HFMSE= hammersmith functional motor scale; aMMO = active maximum mouth opening. [a]All patients with Spinal Muscular Atrphy type 1 in this study survived infancy.

MRI of TMJ and associated muscles

MRI (Figure 4.2, Table 4.3) showed severe to complete atrophy and fatty infiltration of the lateral pterygoid muscle, which is the most important muscle for mouth opening by mediating sliding of the mandibular condyle, in all patients with SMA type 2 and 3a who had reduced aMMO. The anterior belly of the digastric muscles and geniohyoid muscles, involved in the first phase of swallowing and opening of the mouth by depressing the mandible, were moderately affected. In contrast, mouth-closing muscles, i.e. the masseter and temporalis were less affected and the medial pterygoid muscle was relatively spared in all patients (Table 4.2). Fatty infiltration and severe atrophy of the neck extensors were present in patients with and without reduced aMMO. Impaired condylar sliding occurred only in patients with mild-to-severe atrophy and/or fatty infiltration of lateral pterygoid muscles.

In two out of 3 patients with SMA types 3b/4 and normal aMMO, MRI assessment did not show any abnormality of the muscles involved in mouth opening or closing, whereas the MRI of the third patient showed mild fatty infiltration of the lateral pterygoid mucles.

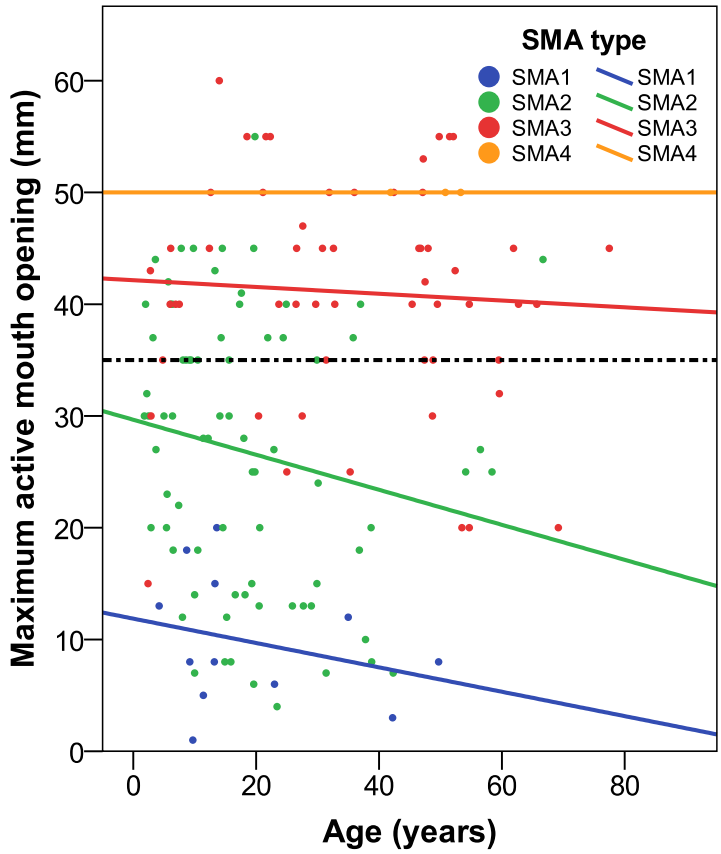

Figure 4.1. Correlation between age and aMMO. Active maximum mouth opening (aMMO) showed a correlation with age in patients with SMA type 1 and 2 (spearman's rho -0.25, p = 0.02). The decline in patients with SMA type 3 with age was not significant (spearman's rho -0.79, p = 0.56). The dotted line represents the lower limit of normal of aMMO (35 mm).

Table 4.2. Characteristics of healthy controls

	Healthy controls			
	All (n=119)	Children <10 years (n=23)	Children 10-18 years (n=40)	Adults (n=56)
Gender F:M	58:61	11:12	18:22	28:28
Mean age, yrs	12	7	14	24
(range)	(5 – 41)	(5 – 9)	(10 – 17)	(18 – 41)
aMMO, mm	51	48	50	53
(range)	(38 – 65)	(38 – 54)	(42 – 60)	(40 – 65)

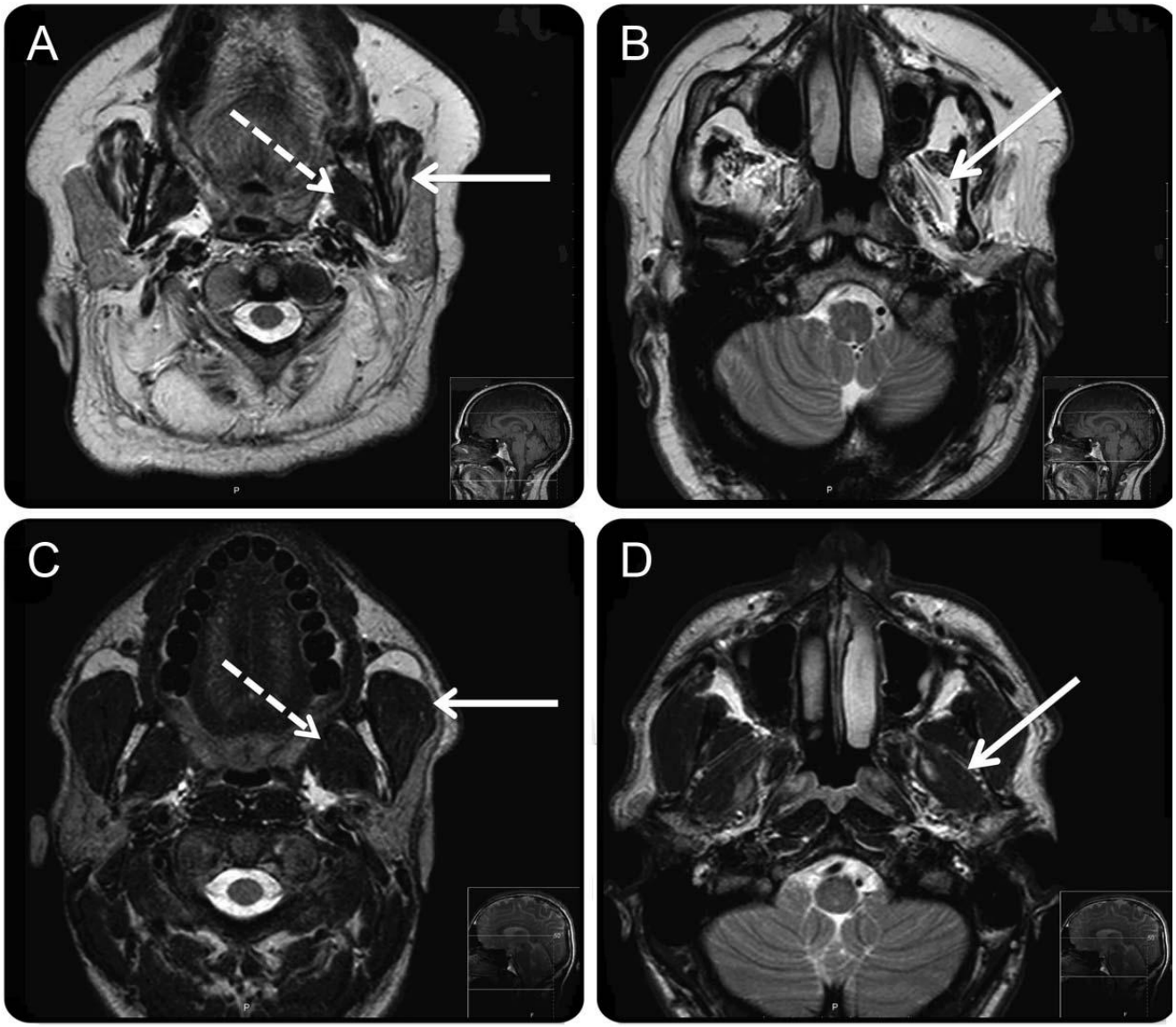

Figure 4.2. MRI of bulbar muscles in a patient with SMA and a healthy control.

Representative T2 Weighted MR Imaging results of patient 3 with SMA type 2 (panels A-B) and subject 13, a healthy control (panels C-D). Left panels (A and C) show masseter (closed arrow) and medial pterygoid muscles (dotted arrow); right panels (B and D) show lateral pterygoid muscles (arrow). Note the severe atrophy and fatty infiltration of lateral pterygoid muscles and mild abnormalities in medial pterygoid muscles and masseter in patient 3 compared to the normal aspect of all muscles in the control (subject 13).

Table 4.3. MR Imaging patient characteristics

	Spinal muscular atrophy												
	Type 2					Type 3						Type 4	Control
	1	2	3	4	5	6	7	8	9	10	11	12	13
Disease duration, yrs	**55.7**	16.8	36.7	23.6	29.4	33.6	45.3	25.5	18.7	28.7	26.3	10.8	NA
MRC sum score	99	96	55	113	76	95	112	141	123	142	141	148	0
HFSME	1	2	0	6	2	0	4	22	18	47	32	43	0
aMMO, mm	25	28	10	40	15	25	45	30	30	45	42	50	50
Neck muscle score	3	3	3	2	3	2	2	1	2	0	0	1	0
Lateral pterygoid score	1	2	3	1	3	2	1	1	2	0	1	0	0
Masseter score	1	1	2	1	2	2	0	0	1	0	0	0	0
Temporalis score	0	2	2	1	2	2	0	0	1	0	0	0	0
Geniohyoid score	0	1	1	0	2	1	1	0	1	0	0	0	0
Digastric score	1	1	1	0	1	1	1	0	1	0	0	0	0
Medial pterygoid score	0	1	1	0	1	0	0	0	1	0	0	0	0
TMJ Condylar sliding	1	1	1	0	1	1	0	0	1	0	0	0	0
Condylar surface	0	0	0	0	0	0	0	0	0	0	0	0	0

Legend: aMMO= active maximum Mouth Opening; MRC= Medical Research Council; HFMSE= Hammersmith Functional Motor Scale Expanded; TMJ= temporomandibular joint; Scores used for fatty degeneration of bulbar muscles; 0 = normal; 1 = mild atrophy or fatty infiltration; 2 = severe atrophy or fatty infiltration; 3 = complete atrophy or fatty infiltration. Condylar surface and condylar sliding were assessed on a two point scale: 0 = normal and 1 = abnormal.

Association of reduced aMMO with dysphagia, eating problems and choking

The presence of fasciculations in the tongue, dysphagia, eating problems or choking events and characteristics associated with disease severity, including SMA type, age at onset, MRC score of the neck flexors and extensors, HFMSE and MRC sum scores, correlated with aMMO in univariate linear regression analysis (all $p < 0.05$). Dysphagia was associated with muscle weakness of the neck muscles (log regression $p < 0.001$). Multivariate linear regression analyses showed that reduced aMMO ($p = 0.01$) and lower MRC sum score ($p = 0.01$) in SMA types 1 and 2 were determinants of dysphagia. ROC analysis showed fair predictive value (PV) of the presence of dysphagia for reduced aMMO (area under the curve, AUC 0.71) or MRC sum score (AUC 0.77) and good PV for HFMSE (AUC 0.81) (Figure 4.3).

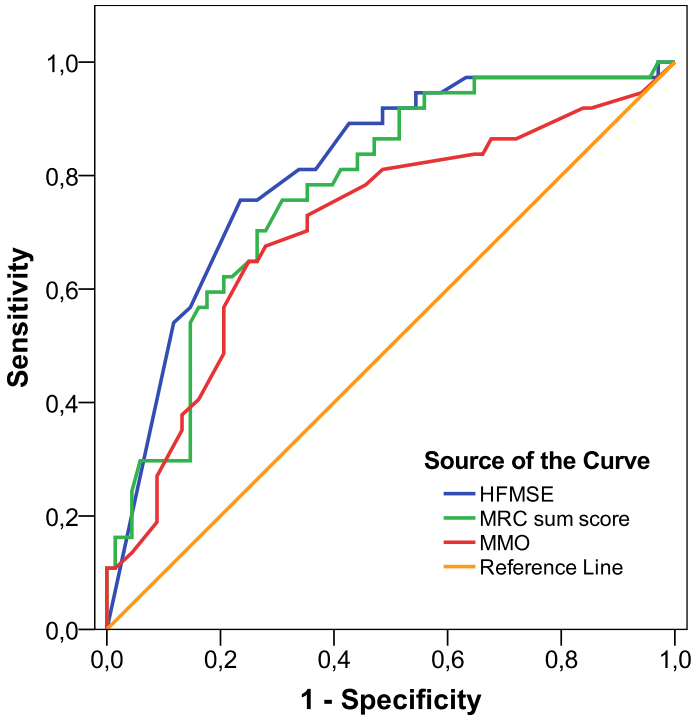

Figure 4.3. Prediction of presence of dysphagia. ROC curves of clinical scores (MRC score, HFMSE and aMMO) reflecting their respective predictive values for the presence of dysphagia. HFMSE area under the curve (AUC) 0.81, MRC sum score AUC 0.77 and aMMO AUC 0.71. Cut-off value for reduced aMMO was set at 35 mm.

Discussion

Reduced aMMO is a common complication in patients with SMA, in particular those with SMA types 1 and 2. MRI of bulbar muscles in 12 patients showed that reduced aMMO is caused by impaired condylar sliding due to severe fatty degeneration of the lateral pterygoid muscles with relative sparing of muscles that mediate mouth closing. Reduced aMMO is associated with self-reported chewing difficulties, frequent choking and dysphagia suggesting that it may reflect a more general process of bulbar motor neuron degeneration in patients with SMA.

Few studies have investigated the cause and impact of dysfunction of bulbar muscles in patients with SMA.[7-11, 14] Evidence for the involvement of bulbar motor neurons comes from clinical and pathological observations, e.g. the frequent finding of fasciculation in the tongue and post-mortem studies that showed degeneration of motor nuclei in the brainstem of severely affected patients.[7-9] Several surveys furthermore reported a high frequency of feeding difficulties and dysphagia.[10, 11, 14] The current view is that dysphagia is a multifactorial complication to which both weakness of bulbar and neck extensor muscles contribute.[10-15] This is compatible with the pattern of fatty degeneration of the anterior digastric, geniohyoid

and neck muscles on the MRI scans of our patients. Mouth opening and closing are mediated by a relatively limited number of muscle groups in comparison to swallowing and limitations in mouth opening may therefore more accurately reflect involvement of bulbar motor nuclei in SMA pathogenesis than dysphagia.

Strengths of this study are the large number of patients of all ages encompassing nearly the full clinical spectrum of SMA, the large control group and the approach of MRI. It should be noted that patients with SMA type 1 included in this study were unusual in the sense that they all survived infancy and represent a subgroup of patients with long survival as reported previously[3, 19-22] We used a strict definition of reduced aMMO (i.e. ≤ 35mm), based on the aMMO range in 119 Dutch healthy individuals, which virtually precludes the possibility that we overestimated prevalence of reduced aMMO. Similar definitions for healthy individuals, varying between 40 – 44 mm for men, 38 – 42 mm for women and 35 – 38 mm for children, were used in previous studies.[23-25] Our prevalence figure of reduced aMMO is nevertheless higher than reported in previous studies. Limitations in mouth opening were self-reported by only 30% of Italian patients with SMA type 2 and 11% of Taiwanese patients with SMA types 2 and 3.[10, 11] Many Dutch patients were not aware that they had a significantly reduced aMMO, which implies that previous self-reporting surveys may have led to underestimation of the true prevalence. This may be partially explained by gradual adaptation to slow progression. Progression of aMMO limitations is suggested by the correlation of reduced aMMO with advancing age and longer disease duration, but this should be established in longitudinal studies.

MRI is a useful technique to document specific patterns of fatty degeneration and atrophy in myopathies and other neuromuscular disorders and yields sufficient anatomical detail of the TMJ.[26] In patients with reduced aMMO, MRI showed normal condylar shape but impaired condylar sliding and marked fatty degeneration and atrophy of the lateral pterygoid muscles. Muscles that mediate mouth closing, i.e. the masseter, temporalis and medial pterygoid muscles and other muscle groups than the lateral pterygoid muscles that mediate mouth opening, i.e. the anterior digastric and geniohyoid muscles, were relatively spared. This pattern explains the reduction in mandibular protrusion, laterotrusion and maximum opening of the jaw that was previously reported in patients with SMA.[13, 15] Normal aMMO is achieved through a combination of rotation, mediated by the submandibular muscles which allows the first 20–30 mm mouth opening and condylar sliding that in combination with further rotation allows for a mouth opening up to 50–60 mm in healthy individuals. The lateral pterygoid muscles mediate condylar sliding and thereby horizontal mandibular movements and

counteract the retrusive forces of the geniohyoid and anterior digastric muscles during mouth opening, thus allowing mouth opening beyond 25–30 mm. Fatty degeneration and atrophy of the lateral pterygoid muscles will therefore lead to reduced or total absence of condylar sliding, causing severely reduced aMMO. aMMO of 20 mm or less is often associated with intra-articular pathology such as adhesions. This may occur secondary to significant degeneration of the lateral pterygoid muscle as suggested by the abnormal TMJ mobility in patients with SMA and severely reduced aMMO (i.e. Table 4.2, patients 1 – 3, 5, 6 and 9).

Post-mortem studies showed degeneration of motor neurons in the brainstem of patients with SMA with a caudo-cranial gradient. The trigeminal motor nucleus was affected in patients with severe SMA, but less than lower cranial nerve nuclei.[7] The high prevalence of reduced aMMO in patients with SMA suggests that motor neuron loss in the trigeminal nucleus is probably more common than reported in previous pathological studies. We can only speculate what causes the specific pattern of bulbar muscle involvement. Differences in motor unit size might explain differences in muscle atrophy and degeneration. Alternatively, specific motor neuron pools or specific bulbar muscle groups may differ in vulnerability to SMN deficiency.

A weakness of our study is the fact that we used a questionnaire, which has been used previously in SMA studies, rather than video-fluoroscopy (VFSS) to assess the presence and severity of swallowing difficulties. Longitudinal studies using both MRI and VFSS in a larger number of patients are needed to investigate the natural history of changes in bulbar muscle composition and function in relation to aMMO and dysphagia. We did not include children with SMA and can therefore not conclude at which age muscle changes start to occur. Finally, we did not perform follow-up MRI to analyze the speed of progression of atrophy and fatty degeneration.[14]

Dysphagia or choking were reported by 35% of our patients with reduced aMMO, figures slightly higher than in previous reports, but nevertheless self-reporting may not be sufficiently sensitive to detect early symptoms of dysphagia and swallowing problems.[10, 11] Reduced aMMO may compromise eating and interfere with maintaining body weight, oral hygiene, and dental and medical care. One of our patients (39 years of age) with a aMMO of 8 mm experienced that intubation prior to elective surgery had become impossible. This shows that reduced aMMO affects patient safety and quality of life and that efficacy of interventions that prevent progression should be investigated. A second reason why measuring aMMO should be incorporated in the follow-up of patients with SMA is the finding that reduced aMMO is associated with an increased risk of dysphagia and choking. ROC characteristics of

aMMO suggest that it may represent an easy tool to assess the risk of involvement of bulbar muscle groups and dysphagia in patients with SMA, but this needs further study.

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PART II

Duchenne muscular dystrophy

Chapter 5

Predictive factors for masticatory performance in Duchenne muscular dystrophy

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Abstract

Objectives: Patients with Duchenne muscular dystrophy (DMD) report masticatory and swallowing problems. Such problems may cause complications (e.g. choking, the feeling of sticking food in the throat). We investigated whether masticatory performance in DMD is objectively impaired, and explored predictive factors for compromised mastication.

Methods: Twenty-three patients and 23 controls filled out two questionnaires about mandibular function, and underwent a clinical examination of the masticatory system and measurements of anterior bite force and masticatory performance. In the patients, moreover, quantitative ultrasound of the tongue and Motor Function Measurement (MFM) was performed. The patients were categorized into ambulatory stage (early or late), early non-ambulatory stage, or late non-ambulatory stage.

Results: Masticatory performance, anterior bite force and occlusal contacts were all reduced in the patient group compared to the controls (all $p < 0.001$). Mastication abnormalities were present early in the disease process prior to a reduction of MFM. The early non-ambulatory and late non-ambulatory stage groups showed less masticatory performance compared to the ambulatory stage group ($p < 0.028$ and $p < 0.010$, respectively). Multiple linear regression analysis revealed that stage of the disease was the strongest independent risk factor for the masticatory performance ($R^2 = 0.52$).

Conclusions: Anterior bite force, occlusal contacts and masticatory performance in DMD are severely reduced.

Introduction

The most prevalent type of muscular dystrophy in children is Duchenne Muscular Dystrophy (DMD), which is characterized by a progressive loss of muscle cells and replacement by fat and connective tissue .[1] DMD is an X-linked recessive disorder or is a consequence of de novo gene mutation. It is caused by a defective gene for dystrophin, an essential component of the dystrophin–glycoprotein complex (DGC) maintaining the membrane integrity of muscle fibers.[2] DMD has an incidence of about 1: 3500 live male births.[3] The onset of DMD symptoms occurs at around 2 to 6 years of age. Untreated, muscle strength deteriorates, and boys require the use of a wheelchair before their teens.[4]

Medical care for patients with DMD, which encompasses medical, surgical, and rehabilitation approaches, has improved the quality and duration of life. As a consequence of the increased duration of life, the non-fatal medical complications of the disease, among which mastication and swallowing difficulties, are now requiring more attention.[5]

The subjective experience of mastication and feeding problems in DMD has previously been documented using questionnaires, yet not objectively using masticatory performance tests. Mastication problems may induce post swallow residue, which has been suggested to possibly contribute to a greater risk of food aspiration.[6-9] Video fluoroscopic swallow studies showed an increased pharyngeal post swallow residue of solid food in advanced stages of DMD.[10]

In general, the dominant factors influencing masticatory performance are the number of occlusal contacts and bite force.[11] Furthermore tongue function is of importance because of its role in food-bolus mixing and positioning.[12] Since masticatory performance of DMD patients has so far not been assessed objectively, it is yet unclear which factors influence the masticatory performance in these patients.

The aim of this study is to compare the masticatory performance of patients with DMD and an age matched healthy control group, and to assess predictive factors for the masticatory performance.

Methods

The study was approved by the Committee on Research Involving Human Subjects of Arnhem and Nijmegen, the Netherlands (registration number 2009/331).

Participants

A case-control study design was used. Twenty-four patients with DMD from 6 to 38 years,

and 24 age-matched male healthy controls were recruited between May 2010 and February 2012. Age limits were set above 5 years to ensure that the participants were capable of undergoing all physical examinations and of filling out questionnaires, whenever needed with the help of their caretakers.

The patients with DMD originate from the cohort of the swallowing study of van den Engel-Hoek et al. 2013.[11] They were recruited by announcements of patient organizations. These patients had a genetically confirmed diagnosis of DMD, or a diagnosis of DMD as defined by the onset of symptoms and disease course of DMD. DMD patients who were entirely dependent on tube feeding were excluded.

The control group was recruited at a primary and a secondary school located in the western part of the Netherlands, and consisted of children and parents. Controls above 18 years were as well recruited at the College of Dental Sciences, Nijmegen, the Netherlands. Exclusion criteria for healthy controls were: a history of neuromuscular disease, temporomandibular disorder, orthodontic treatment and the morphologic dental malocclusions cross bite or tendency to cross bite.

Eligible participants and their parents were sent information letters with an invitation to participate in the study. After receiving informed consent from the adults or parents, and – if the subjects were older than 12 years – also from the participants, the participants underwent all examinations in the hospital during one day.

Protocol

The participants in both the patient and the control group, completed structured questionnaires, and underwent a clinical examination of the masticatory system, anterior maximum voluntary bite force (MVBF) and food mixing ability measurements. Additionally, the patients underwent quantitative muscle ultrasound imaging (QMUS) of the tongue, and an assessment of their general physical abilities.[13]

Questionnaires

The patient group and the control group completed two questionnaires: Screen and the Mandibular Functional Impairment Questionnaire (MFIQ).[14-16] Screen contains questions related to: (1) quantitative and qualitative aspects of pain in the head, neck and shoulders such as the pain location(s) (which the patient could mark on a drawing of the head, neck and shoulders), the pain intensity as reported on a Visual Analogue Scale (VAS), and factors influencing pain; (2) symptoms of temporomandibular dysfunction such as joint noises,

limited mouth opening and mastication difficulties; (3) oral habits, such as tooth-grinding and clenching; and (4) general health factors (e.g. medication, family history). MFIQ was designed to measure impairments of the function of the masticatory system. MFIQ consists of 17 questions, which can be subdivided into two dimensions - functional capacity and feeding, and is rated on a 5-point Likert scale ranging from '0' (no difficulty) to '4' (very difficult or impossible without help). The ratings are added to give a sum score (S, range 0–68). A higher score indicates more perceived mandibular function impairments and a MFIQ score of '0' indicates no impairment in mandibular functioning. The raw score of the MFIQ-scale (C, range 0–1) is obtained by dividing the sum of the items by four times the number of the items (C = S/68). The raw score can be converted to a qualitative level of impairment: no/low (I), moderate (II) and high (III). Previous studies have considered the MFIQ to be a reliable and valid tool.[17]

Clinical examination of the masticatory system

All participants in this study were clinically examined following a validated procedure as described by Lobbezoo-Scholte et al. (1993, 1994).[18,19] This clinical examination included, among others, measurement of the mandibular range of motion, palpation of the masticatory muscles and the temporomandibular joints and the number of occlusal contacts (OC-score). Moreover, the dental occlusion of the participants was evaluated regarding (tendency to) cross bite. OC-scores between the premolar and molar teeth of the upper and lower jaw after the teeth were brought into occlusion were assessed using wax records (Moyco beauty pink plate wax, 2270 g). A perforation in the wax record indicated an occlusal contact. Unilaterally, the maximum OC-score is 5 (1 OC per posterior occluding pair); bilaterally the maximum is 10. The dental occlusion, defined as the static relationship between the masticating surfaces of the maxillary or mandibular posterior teeth, was assessed regarding the presence or absence of uni- or bilateral abnormal transverse relationship of single or multiple posterior teeth (i.e., premolars or molars). Tendency to cross bite was noted when the maxillary and mandibular (pre)molar(s) were in cusp-to-cusp occlusion (Figure 5.1). Cross bite was noted when the maxillary posterior teeth are in lingual position in relation to the mandibular posterior teeth (Figure 5.1).

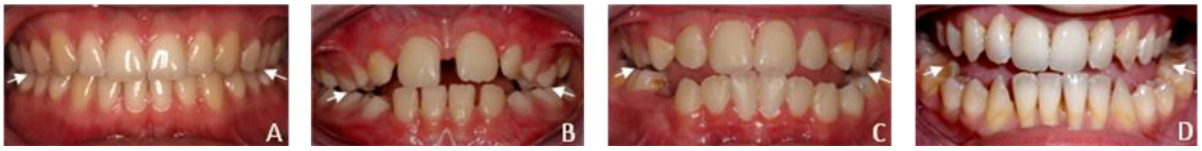

Figure 5.1. Dentition in maximal intercuspal position. Dentition of a healthy subject (A), and 3 patients with DMD; ambulatory stage (AS) (B), early non-ambulatory stage (ENAS) (C), late non-ambulatory stage (LNAS) (D). (A) Healthy subject; age 14; occlusal contacts 8; no cross bite L/R (see arrow). (B) AS; age 8; occlusal contacts 3; tendency to cross bite L/ R. (C) ENAS; age 11; occlusal contacts 2; cross bite L/ R. (D) LNAS; age 21; occlusal contacts 2; cross bite L/ R.

Measurement of the anterior maximum voluntary bite force

To measure the bite force, the VU University Bite Force Gauge (VU-BFG) was used.[20] It is a handheld device which uses a load cell (LPM 510 250lb) to measure maximum voluntary bite force (MVBF) in kg. The handheld device consists of a strain gauge mounted on a mouthpiece which is 11 mm high and 15 mm wide. The VU-BFG measures bite forces ranging between 0 to 490 N in a linear fashion. The bite force transducer was calibrated at the VU University Amsterdam, the Netherlands, before, half way and at the end of the data collection. Measurements were taken using the following protocol. The strain gauge element was placed parallel with the Frankforter horizontal, between the upper and lower central incisors and midway between the central maxillary incisors, with the metal edge mounted on the top surface of the mouthpiece against the upper central incisors. Patients and controls clenched as hard as possible for 3 seconds, during which the peak maximum bite force was recorded. They repeated clenching three times with an interval of 30 seconds rest periods; the highest value of the three measurements was used as the anterior MVBF. The participants were instructed in a similar way, by repeating the words 'as hard as possible' three times. The similar procedure was performed between the upper and lower canines on the left and right side.

Mixing ability test

In all participants, masticatory performance was measured using the mixing ability test.[21] A wax tablet consisting of a red and a blue wax layer was offered to the subjects (tablet at room temperature, 20 °C). Each participant performed 20 chewing strokes on a tablet, and as a result the colours would mix. The degree of mixing represented the masticatory performance. The chewed wax is flattened and photographed from both sides with a high-quality scanner (Epson_ V750, Long Beach, CA, USA). The spread of the colour intensities in the combined

image of both sides is the measure of mixing. The images of the wax are processed using Adobe Photoshop, CS3 extended (Adobe, San Jose, CA, USA). The intensity distributions of the red and blue channels are exported as 8-bit histograms. The histograms of both sides of the wax are added to obtain the red and blue intensity distributions of the combined image of both sides of the flattened wax. These histograms are analyzed to obtain a measure for the mixing of the wax: the mixing index.

Echo intensity imaging of the tongue

In the patient group, QMUS was used to measure echo intensity of the longitudinal superior and transverse tongue muscles, and thickness of the tongue.[13] The region of interest was quantified by grey-scale analysis and calculation of z scores (i.e. the amount of standard deviations below or above the mean of norm values); a reliable method in which changes in muscle architecture are assessed and compared with norm values.[22] QMUS of the tongue proved to be feasible in healthy children and young adults, and is used for detection of structural changes of, among others, tongue muscles.[13]

Medical information and physical abilities

In the patient group, information was gathered about the age of onset of DMD, body mass index, the use of ventilation support, swallowing difficulties, prolonged mealtime, food adaptation and the medication used in previous years (i.e. prednisone, and antibiotic therapy for chest X-ray proven pneumonia in the past year).

Baseline gross motor function was assessed in all patients by a physical therapist with expertise in paediatrics using the Motor Function Measure (MFM). MFM is a quantitative scale that enables measuring the functional motor abilities of a person affected by a neuromuscular disease. MFM consists of 3 domains: D1 standing position and transfers, D2 axial and proximal motor function and D3 distal motor function. In this study, we used items 13 to 23 of domain 2 and 3 which are designed to collect information about the sitting position, arm function, and neck and head control.[23] The items were scored on a four-point Likert scale and summed to comprise a total score expressed as a percentage of the maximum score (range 0–100), in which the maximum represents normal motor function. In this study calculation of the data is performed by using the raw score of the MFM items 13 to 23 (range 0–33).

Based on the ambulatory function and the MFM, the patients were divided in three subgroups: early and late ambulatory stage (AS), early non-ambulatory stage (able to maintain posture) (ENAS), or late non-ambulatory stage (upper limb function and postural maintenance is increasingly limited) (LNAS).[24]

Statistical analysis

IBM SPSS version 20 was used to analyse the collected data. The level of significance was set at $p = 0.05$. Descriptive statistics in terms of mean and standard deviation were used to describe the independent scale variables in the patient and control group. Paired Student's t-test was used to compare between-group continuous variable outcomes, and for dichotomous variables the chi-square test was used.

The collected data within the patient group were further analysed using the 3 DMD stages. To compare test outcomes between the DMD stages ANOVA was used for scale variables and chi-square test for dichotomous variables.

Univariate linear regression analyses were performed to determine which factors (independent variables) possibly affect the mixing ability in the patient group (dependent variable). The independent variables were age, ambulatory stage, anterior MVBF, OC score, QMUS of the tongue and tongue thickness. The independent variables, which were possibly associated with the mixing ability ($p < 0.01$) were included in a multiple linear regression analysis (stepwise backward method; p-value to remove > 0.05) in order to determine the set of variables that best predict impaired chewing in DMD patients.

Results

Participants

Twenty-four patients with DMD were approached for inclusion in the study. One of the patients was excluded from the study because DMD was not genetically confirmed, and the signs and symptoms did not fit into the DMD diagnosis. For analysis, the data of 23 patients and 23 age-matched male controls were used (Table 5.1). Patient characteristics of the total DMD sample as well as of the three stage groups can be seen in Table 5.2.

Table 5.1. Group comparison and descriptive statistics of the anterior maximum voluntary bite force (MVBF) in Newton and mixing ability during clinical examination in the patient group (MVBF, n = 23; mixing ability, n = 22) and in the control group (MVBF and mixing ability, n = 23). Mean and standard deviation of the measurements are referred to as $\bar{x}$ (SD).

Clinical examination	Patient group	Control group	P-value
Age	16.7 (7.7)	16.3 (6.7)	0.851
range	6.3 – 38.1	6.1 – 30.2	
Mixing ability[a]	25.1 (3.7)	18.2 (2.8)	<0.001*
range	17.3 – 30.2	12.7 – 22.8	
Anterior MVBF[b]	87.5 (35.5)	160.6 (88.4)	0.001*
range	10.8 – 171.6	43.1 – 332.4	
Occlusal contacts	3.2 (2.4)	6.8 (1.3)	<0.001*
range	0 – 8	4 – 8	

* = Statistically significant differences.

[a]Mixing ability: individual's capacity to grind a two colored wax tablet during 20 strokes of chewing (n = 22 in patient group).

[b]Anterior MVBF: maximum vertical interocclusal bite forces between the central incisors of the upper and lower jaw.

Questionnaires

Screen and anamnestic information

Thirteen patients (57%) mentioned mastication difficulties. In two patients, the mastication problems interfered with daily and social activities. Prolonged meal-time (> 30 min.) was reported during history taking by patients, parents or caretakers in 15 patients (65%). Swallowing difficulties were reported by 15 patients (65%) (Table 5.2). The controls did not report mastication difficulties.

Mandibular Function Impairment Questionnaire

One patient (4%) reported severe mandibular function impairment, 7 (30%) a moderate impairment, and 15 patients (65%) reported no/low impairment. There was a statistically significant difference between the ENAS and LNAS and between the AS and LNAS in terms of mandibular function. Information on food adaptation by the patients, derived from the MFIQ showed that 12 patients (52%) had to adjust their food (Table 5.2). There was a significant correlation between the reported food adaptation and prolonged mealtimes

($p = 0.009$). The controls did not report impairment of the mandibular function.

Clinical examination of the masticatory system

The OC score in the posterior teeth of the upper and lower jaws was reduced in > 50% of the patients (average OC score 3.2, SD 2.4, range 4–8) compared with the controls (average OC score 6.8, SD 1.3, range 0–8) (Table 5.1). In the patient group, reported mastication difficulties ($p = 0.008$), more masticatory functional impairment ($p < 0.001$), a thicker tongue ($p = 0.001$) and increased echo intensity of the longitudinal tongue muscle ($p = 0.016$) correlated with less occlusal contacts.

In the patient group, 23 (100%) showed malocclusions; lateral cross bites on the left and/or right side were present in 17 patients (74%) and tendency to cross bite in 6 patients (26%) (Table 5.2). (Tendency to) cross bite is highly prevalent already in the AS group (viz., in 100% of the AS patients there was either a tendency to cross bite or a full cross bite), while MFM-score in this group is hardly reduced (MFM score 98.2).

Maximum voluntary bite force

The anterior MVBF was significantly weaker in the patient group compared with the control group (Table 5.1). The DMD group was able to exert an average anterior MVBF of 87.3 N (SD 35.3, range 10.8 – 171.6 N), compared with 160.8 N (SD 88.3, range 43.4 – 332.4 N) for the control group. In the control group the MVBF was not significant correlated with age ($p = 0.106$).

Mixing ability test

One out of 23 patients was excluded from this analysis because of fear to choke when chewing the tablet. The masticatory performance was significantly worse in the patient group (mean mixing ability index 25.1, SD 3.7) compared with the control group (mean mixing ability index 18.2, SD 2.8) (Table 5.1). There was a statistically significant difference between the ENAS and LNAS in terms of masticatory performance (Table 5.2).

Imaging of the tongue

The echo intensity of the tongue muscles, expressed as z-score, showed a gradual increase among the three DMD stages; mainly in the LNAS echo intensity of the tongue was increased ($z > 2$). There was a statistically significant difference between the ENAS and LNAS and between the AS and LNAS regarding the superior longitudinal and transverse muscle of the

tongue (Table 5.2).

Tongue thickness in the AS was for all patients within the normal range (z-score <2), but not in the ENAS and LNAS (Table 5.2). There was a statistically significant difference between the AS and ENAS and AS and LNAS in terms of tongue thickness (Table 5.2). Tongue thickness and OC score were significantly negatively correlated ($p = 0.001$).

Physical abilities

In our patient group, the measures of motor function by MFM showed a decline with losing the ambulatory function. There was a significant difference in the MFM score between the ENAS and LNAS and AS and LNAS regarding the MFM total score (Table 5.2).

Predictive factors for masticatory performance

Univariate linear regression analysis of potential determinant of compromised masticatory performance are indicated in Table 5.3. The univariate linear regression analysis revealed a negative correlation between masticatory performance and DMD stage (ENAS), and the anterior maximum voluntary bite force. Multiple linear regression analysis revealed ENAS DMD stage to be the most significant factor for masticatory performance ($R^2 = 0.52$, Table 5.4).

Table 5.2. Characteristics of patients with Duchenne muscular dystrophy (n = 23) presented by stages. Mean and standard deviation of the measurements referred to as $\bar{x}$ (SD) and number of patient as n / %.

		DMD stage			p-value		
	Total (n=23)	AS (1) (n=6)	ENAS (2) (n=7)	LNAS (3) (n=10)	1-2	2-3	1-3
Mean age, yrs.mo	16.7 (7.7)	8.4 (1.5)	15.0 (4.1)	22.8 (6.5)	0.004*	0.014*	<0.001*
range	6.3 – 38.1	6.3 – 10.5	10.7 – 20.6	16.3 – 38.1			
MFM, total score[a]	60.5 (39.0)	98.2 (3.0)	80.9 (25.2)	23.7 (22.7)	0.120	<0.001*	<0.001*
range	0 – 100	93 – 100	30 – 100	0 – 75			
Body mass index	20 (5.0)	16.3 (1.9)	22.1 (4.7)	20.8 (5.4)	0.023*	0.624	0.089
range (kg / m^2)	14 – 35	14 – 20	16 – 29	15 – 35			
MFIQ raw score[b]	0.23 (0.17)	0.1 (0.12)	0.2 (0.12)	0.4 (0.15)	0.707	0.009*	0.007*
range	0.36 – 0.31	0.02 – 0.34	0.02 – 0.35	0.12 – 0.56			
Anterior MVBF	87.3 (35.3)	97.1 (26.5)	101.0 (37.3)	73.5 (35.3)	0.876	0.161	0.268
range (N)	10.8 – 171.6	71.6 – 123.6	60.8 – 171.6	10.8 – 171.6			
Mixing ability	25.4 (3.9)	24.5 (5.1)	22.6 (2.3)	28.3 (2.0)	0.415	0.001*	0.254
range	17.2 – 30.2	17.2 – 29.0	20.7 – 26.5	24.2 – 30.2			
Occlusal contacts	3.2 (2.4)	5.3 (2.0)	3.9 (2.0)	1.4 (1.7)	0.203	0.013*	0.001*
range	4 – 8	3 – 8	2 – 7	0 – 5			
EI superior long m[c]	1.6 (2.3)	-0.03 (0.8)	0.67 (0.9)	3.3 (2.6)	0.175	0.014*	0.003*
range	-1.1 – 6.2	-1.1 – 0.9	-0.8 – 2.2	-2.0 – 6.2			
EI transversus m[c]	0.6 (1.6)	-0.1 (1.7)	-0.2 (1.1)	1.6 (1.4)	0.876	0.012*	0.048*
range	0.0 – 1.3	-1.7 – 2.1	-1.6 – 1.6	0.7 – 2.5			
Tongue thickness[d]	2.8 (2.4)	1.1 (0.4)	2.8 (1.7)	3.7 (3.0)	0.039*	0.446	0.022*
range	0.6 – 1.7	0.6 – 1.7	0.08 – 5.44	-0.19 – 9.43			
Prednisone[e]	10 / 44%	5 / 83%	4 / 75%	1 / 10%	0.012*		
Antibiotics[f]	7 / 30%	0 / 0%	1 / 14%	6 / 60%	0.031*		
Ventilatory support					<0.001*		
None	13 / 57%	6 / 100%	6 / 86%	1 / 10%			
Part-time (nocturnal)	6 / 26%	0 / 0%	1 / 14%	5 / 50%			
Continuous noninvasive	3 / 13%	0 / 0%	0 / 0%	3 / 30%			
Continuous + tracheostomy	1 / 4%	0 / 0%	0 / 0%	1 / 10%			
Mastication difficulties[g]	13 /57%	3 / 50%	4 / 57%	6 / 60%	0.926		
Posterior occlusion							
cross bite	17 / 74%	1 / 17%	6 / 86%	10 / 100%	<0.001*		
tendency to cross bite	6 / 26%	5 / 83%	1 / 17%	0 / 0%	0.001*		
Prolonged mealtime[h]	15 / 65%	3 / 50%	3 / 43%	9 / 90%	0.088		
Swallowing difficulties[i]	15 / 65%	4 / 67%	3 / 43%	8 / 80%	0.288		
Food adaptation[l]	12 / 52%	1 / 17%	3 / 43%	8 / 80%	0.041*		

* = Statistically significant differences; DMD = Duchenne Muscular Dystrophy; AS = Early and late ambulatory stage; ENAS = Early non-ambulatory stage; LNAS = Late non-ambulatory stage.

[a]MFM: Motor Function Measure, domain 2, items 13 to 23 assessed axial en proximal motor capacities –12 items (total score 33 points = 100%); MFM score per item: 0 = does not initiate movement or starting position cannot be maintained; 1 = partially completes the exercise; 2 = completes the exercise with compensations, slowness or obvious clumsiness; 3 = completes the exercise with a standard pattern.

[b]MFIQ raw score: seventeen questions with answers on a five-point Likert scale, to assess the extent of the difficulties experienced to perform a particular mandibular task. The total score is the score of the degree of masticatory and non-masticatory impairment that represents the total function impairment. The total score of the scale (C) is the sum of the 17 items (S) divided by 4 times the number of items (n): C = S / 4n.

[c]EI: muscle echo intensity gray value (z-score) of the image of the superior longitudinal muscle and the transversus muscle of the tongue; z-score > 2.0 is considered as abnormal echo intensity (Engel-Hoek et al., 2012).

[d]Tongue thickness: the thickness of the tongue, including the geniohyoid and genioglossal muscles, was measured from the raphe of the mylohoid muscle to the upper boundary of the tongue (Engel-Hoek et al., 2012).

[e]Prednisone: % of patients using prednisone at base line or previously.

[f]Antibiotics: patients with pneumonia in need of ≥ 1 antibiotic medication in the past year.

[g]astication difficulties: rated on a 5-point scale. 0 = never; 1 = sometimes; 2 = regularly; 3 = often; 4 = very often. Patients with a score > 1 are considered to have mastication difficulties.

[h]Prolonged meal time: rated on a 5-point scale. 0 = normal; 1 = sometimes > 30 minutes; 2 = always > 30 minutes; 3 = > 45 minutes; 4 = > 60 minutes. Patients with a score >1 are considered to have prolonged meal time.

[i]Swallowing difficulties: rated on a 5-point scale. 0 = never; 1 = sometimes; 2 = regularly; 3 = often; 4 = not applicable. Patients with a score > 1 are considered to have difficulty in passing the food from the mouth into the stomach.

[j]Food adaptation: patients unable to eat hard biscuits, meat, raw carrots, French loaf or nuts.

Table 5.3. Univariate linear regression analysis of determinants for food mixing ability in Duchenne muscular dystrophy patients

Model	Effect	95 % Confidence Interval for Effect		p-value	R^2
		Lower Bound	Upper Bound		
Age (in years)	0.08	-0.136	0.30	0.449	0.03
Ambulatory stage					0.32
LNAS	Reference				
AS	-2,76	-6.29	0.77	0.119	
ENAS	-4,70	-8.08	-1.33	0.009*	
Anterior MVBF	-0.04	-0.09	-0.00	0.004*	0.20
OC	-0.40	-1.10	0.30	0.247	0.07
EI superior longitudinal tongue muscle (z-score)	0.35	-0.35	1.05	0.310	0.05
EI transverse tongue muscle (z-score)	0.30	-0.74	1.34	0.554	0.01
Tongue thickness (z-score)	-0.13	-0.89	0.62	0.714	0.00

* = Statistically significant differences.

Table 5.4. Multiple linear regression analysis of determinants for food mixing ability in Duchenne muscular dystrophy patients

Model	Effect	95 % Confidence Interval for Effect		p-value.
		Lower Bound	Upper Bound	
(Constant)	35.2	26.8	43.5	<0.001*
Age (in years)	-0.22	-0.51	0.73	0.131
Ambulatory stage				
LNAS	Reference			
AS	-4.0	-9.6	1.5	0.143
ENAS	-5.6	-9.4	-1.7	0.008*
Anterior MVBF	-0.37	-0.78	0.04	0.076

R^2 = 0.52; * = Statistically significant differences.

Discussion

In this study, the impact of DMD on the masticatory system was assessed by comparing the masticatory performance of patients with those of a gender and age matched healthy control group. Also, masticatory function per ambulatory stage (AS, ENAS or LNAS) in the DMD group was examined. Predictive factors were established for masticatory performance in the patient group. This study shows that masticatory performance, anterior MVBF and OC score were significantly lower in patients with DMD compared to controls. The reduced masticatory performance in patients with DMD was primarily related to higher disease severity.

In healthy individuals, the relationship between the forces exerted by the masticatory muscles and the tongue on the one side and craniofacial development and development of the dentition on the other side, has been well established.[25,26] The progressive wasting of skeletal muscles in patients with DMD, including the masticatory, facial and tongue muscles, influences the growth and development of the craniofacial skeleton, eventually resulting in a malocclusion.[27-29] These changes may lead to an impaired masticatory performance.

Subjective evaluation of patients with DMD shows that they rate their masticatory performance as compromised.[6,7] Our study confirmed these findings expressed by subjective answers of the patient (Screen and oral history) in most of the cases (Table 5.2). The mastication difficulties are also represented in the MFIQ score: 8 patients (35%) had a moderate to severe mandibular function impairment.

The mixing ability in our patient group was 25.1, which indicates worse performance than in our healthy controls (18.2), and even worse than in otherwise healthy full denture wearers (21.2) measured using the same method by Speksnijder et al. (2009).[21] The lower anterior MVBF in our patients with DMD indicates that the masticatory muscles, especially the mandibular closing muscles, are substantially weaker. This is in agreement with previous studies.[27,29,30] Another important finding in our study is the fact that the weakness of the masticatory muscles starts early in the course of the disease: the AS subgroup already shows a significantly reduced bite force, compared to controls (Table 5.1 and 5.2). This explains the low masticatory performance already in young children with DMD.

One of the important factors influencing the masticatory performance in healthy subjects is the number of occlusal contacts (OC score).[11] Although there is a correlation between the OC score and the subjective reports by the patients regarding their quality of mastication (reduced MFIQ raw score and increased mastication difficulties), the expected correlation between the objective chewing performance and the OC score in our patients with DMD did not reach significance. The absence of this correlation can be explained by the fact

that despite a reduced OC score the patients were still able to mix the colours of wax tablet using an adapted way of chewing. We observed during the mixing ability test that patients with a reduced OC score chewed the wax tablets mostly with their occluding anterior teeth. For this strategy, not the number of occluding (pre)molars, but the anterior bite force seems of importance for the masticatory performance. The latter is corroborated by our finding of albeit weak association between anterior MVBF and the mixing ability (Table 5.3 and 5.4).

We cannot determine whether the decline in mixing ability in the patients with DMD was further influenced by exposure to prednisone. Prednisone-naïve DMD patients are insufficiently represented in AS and ENAS to assess a statistical link between prednisone and masticatory muscle function. Additionally the standard of care for DMD has changed overtime, resulting in a different standard of treatment for LNAS than for the AS and ENAS. Comparing the stage groups is thereby not possible.

In our study, the MVBF was measured between the anterior teeth which is a frequently used and reliable method.[31] The measurements of the MVBF between the canines in the patients and the control subjects were not always feasible because of loose, partly erupted or missing canines due to the transition from primary to secondary dentition. For this reason, the MVBF between the canines is not included in the analyses.

The tongue size and position play a clinically relevant role in the development of malocclusions in healthy individuals.[26,32] In patients with DMD, ultrasound images indicated tongue enlargement as a result of (pseudo) hypertrophic changes early, and progressive dystrophic structural changes late in the disease process.[13] The significant correlation found between the tongue thickness measured by the echo intensity, and the OC score is an expression of the developing occlusal changes already in early stages. It is probably the combination of an enlarged tongue measured with the QMUS, in combination with the weakness of the masseter muscle, expressed by a decrease in MVBF early in the disease process, that caused in our patient group tendency to cross bite and/or cross bite, already in the AS (83% and 17%, respectively).

Previous studies mention that the muscles of the hips, pelvic area, thighs and shoulders are affected first and that the masseter muscles follow the general progress of the disease.[29,32] In our cohort, decrease in the MVBF and dental changes with a corresponding reduction of the OC score were present early in the disease process prior to a reduction of the motor function assessed by the MFM (Table 5.2). This finding, together with previous report on early structural changes in the tongue in AS by van den Engel-Hoek et al. (2013) suggests that the orofacial musculature might be affected earlier in the diseases process than expected.

A reduced masticatory performance might contribute to prolonged meal time and masticatory muscle fatigue. In the LNAS group, all patients reported prolonged duration of food intake. Weight loss becomes a health issue for the patients in this subgroup. Food adaptation (soft or chopped food) is needed to ensure a sufficient calorie intake. In healthy individuals, a softer diet is associated with a reduced bite force, an increased frequency of malocclusion and a negative influence on the masticatory performance.[35] Food adaptation in our patient group had a significant correlation with reported prolonged meal times. It seems that when patients experience mealtime prolongation they decide to adapt their food. We expect that the food adaptation, indicated by the MFIQ and by Screen, may further compromise the masticatory system.

Before indicators can be suggested to use in clinical practice in the decision making regarding dietary adaptation, further research is needed. Until then we suggest that the decision to adapt food should be based on the following requirements: sufficiency of the airway defense mechanisms, cough strength and calorie intake. Our advice is to encourage patients to postpone food adaptation as long as patients meet these requirements which will apply mainly to AS and ENAS. In case the requirements are not met, van den Engel-Hoek et al. (2013) suggest to (1) adjust meals in terms of less solid food and (2) drink water after meals to clear the oropharyngeal area.[10] Moreover, we suggest that masticatory exercises are applied in DMD as early as possible in the disease, for example, at first reports of food adaptation, in an effort to postpone the decline of masticatory muscle function in these patients.

The results of a previous study on boys with DMD as to the effect of low-intensity physical training on preservation of muscle endurance and functional abilities are promising.[36] The correlation of the MVBF with masticatory performance in DMD may offer possibilities for intervention. The masticatory exercise study of Kawazoe et al. (1982) on training the masticatory system in patients with DMD demonstrated an improvement of the masticatory function. However this exercise does not match with the latest training suggestions for patients with muscular dystrophy which are low intensity aerobic exercises.[37] An example of a low intensity aerobic exercise is the use of chewing gum. In healthy individuals, training of the masticatory muscles with chewing gum influenced the functional capacity of these muscles and increased their strength.[38] A training program for the chewing muscles may have a positive effect upon mastication as well, and may lead to improvement, maintenance or a slower decline of the masticatory performance. In this context, training of the masticatory system in patients with DMD could be beneficial.

Conclusion

This study demonstrated that impairment of the masticatory system, expressed as reduced masticatory performance, is common among boys and men with DMD. Early recognition of masticatory limitations is recommended since masticatory performance deteriorates with DMD stage already in early stages of the disease. We suggest that there may be potential beneficial effects of a training program in DMD.

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Chapter 6

Reduced mandibular range of motion in Duchenne Muscular Dystrophy: predictive factors

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Abstract

Objectives: Patients with Duchenne muscular dystrophy (DMD) experience negative effects upon feeding and oral health. We aimed to determine whether the mandibular range of motion in DMD is impaired, and to explore predictive factors for the active maximum mouth opening (aMMO).

Methods: 23 patients with DMD (mean age 16.7±7.7 years) and 23 controls were assessed using a questionnaire about mandibular function and impairments. All participants underwent a clinical examination of the masticatory system, including measurement of mandibular range of motion and variables related to mandibular movements. In all patients, quantitative ultrasound of the digastric muscle and the geniohyoid muscle and the Motor Function Measure (MFM) scale were performed. The patients were divided in early and late ambulatory stage (AS), early non-ambulatory stage (ENAS), and late non-ambulatory stage (LNAS).

Results: All mandibular movements were reduced in the patient group ($p < 0.001$) compared to the controls. Reduction of the aMMO (< 40 mm) was found in 26% of the total patient group. LNAS patients had significantly smaller mandibular movements compared to AS and ENAS ($p < 0.05$). Multiple linear regression analysis for aMMO revealed a positive correlation with the body height and disease progression, with MFM total score as the strongest independent risk factor ($R^2 = 0.71$).

Conclusions: Mandibular movements in DMD are significantly reduced and become more hampered with loss of motor function, including the sitting position, arm function, and neck and head control. We suggest that measurement of the aMMO becomes a part of routine care of patients with DMD.

Introduction

Duchenne muscular dystrophy (DMD) is, with an incidence of about 1: 4200 live male births, one of the most prevalent hereditary muscle diseases.[1] It is caused by a defective gene for dystrophin, a protein that helps to keep muscle cells intact.[2]

DMD is characterized by progressive muscle weakness including the craniofacial muscles.[3,4] The weakness of the craniofacial muscles consequently affects the development and morphology of the craniofacial structures.[5-8] Weakness of the jaw muscles, in combination with changes in the craniofacial morphology may affect mandibular function, including mandibular range of motion (ROM).[4,9] To our knowledge, predictive factors for a compromised mandibular ROM in patients with DMD have not been investigated yet.

The most important influencing factors upon the mandibular ROM in healthy subjects are the length of the mandible, functional capacity of the mandibular opening and closing muscles, morphology and status of the temporomandibular joint (TMJ), and pain conditions in the masticatory system.[9,10]

Ultrasound measurements in patients with DMD of the masseter muscles and the suprahyoid muscles showed structural changes in these muscles indicating muscular dystrophy.[4,11] Hypothetically, the structural changes may lead to decreased strength of the muscles involved in mandibular movement and contribute to a limited mandibular ROM.

Factors beyond the masticatory system may contribute to a reduction of the mandibular ROM as well. Recent observations suggest a functional relationship between the cranio-cervical and the masticatory system.[12,13] As a consequence gross motor function measurement, which includes assessment of posture, neck function, and head control, might be predictive for the mandibular ROM.

The aim of our investigation was to determine whether the mandibular ROM in DMD is impaired compared to that in healthy subjects, and to explore predictive factors for the active maximum mouth opening (aMMO) in DMD.

Methods

Participants

Twenty-four patients with DMD aged from 6 to 38 years, participating in a swallowing study on DMD, and 24 age-matched healthy males were examined between May 2010 and February 2012.[11]

Patients were recruited by announcements of patient organizations. Only patients with an established diagnosis of DMD older than five years were eligible. DMD patients who were entirely dependent on tube feeding were excluded.

The control group was recruited at a primary and a secondary school located in the western part of the Netherlands. Healthy students above 18 years were recruited at the College of Dental Sciences, Nijmegen, The Netherlands. Exclusion criteria for controls were: a history of neuromuscular disease, temporomandibular disorder, orthodontic treatment and morphologic dental malocclusion such as crossbite and a tendency to crossbite.

Protocol

The participants in both the patient and the control group, completed a questionnaire, and underwent a clinical examination of the masticatory system including measurement of the mandibular ROM.

Additionally, the patients underwent quantitative muscle ultrasound imaging (QMUS) of the anterior belly of the digastric muscle and the geniohyoid muscle, and an assessment of their general physical abilities using the Motor Function Measure (MFM).[14,15]

Questionnaire

All subjects completed the questionnaire Screen, which was developed to assess pain in the head and neck region, mandibular function and related issues.[16,17]

Clinical examination of the masticatory system

All participants in this study were clinically examined following the validated procedure as described by Lobbezoo-Scholte et al. (1993, 1994)[18-21] This clinical examination included, among others, measurement of the mandibular range of motion, palpation of the masticatory muscles and the TMJs. All patients and controls were examined in the upright position with their heads supported in a neutral position.

The following mandibular movements were assessed: active maximum mouth opening (aMMO), passive maximum mouth opening (pMMO), protrusion, and left and right lateral ROM. The overbite and overjet were also measured. The aMMO was the distance measured between the mesioincisal angle of the right upper and lower front teeth plus the overbite. All measurements were recorded with a metal ruler (mm). We considered mandibular movements to be reduced: < 40 mm for aMMO, < 8 mm for active lateral ROM and < 5 mm for protrusion. The mobility of the TMJ was assessed by palpation of the lateral pole of the

mandibular condyle during aMMO with the index finger. Sliding of the mandibular condyle was assessed on a 2 point scale: reduced meaning no or hardly any sliding of the lateral pole of the mandibular condyle; normal meaning sliding of the mandibular condyle to the crest of the articular eminence or beyond the crest of the articular eminence.

The masseter and temporalis muscles were palpated to assess pain on palpation. The temporalis muscles were palpated bilaterally by using the index- and middle finger, applying firm pressure along the anterior, middle and posterior parts for 2 to 3 seconds. Then the origin, the body and the insertion of the masseter are individually palpated for 2 to 3 seconds. Finally the TMJs were palpated for 2 to 3 seconds by using the index finger. The left and right condyles were palpated in an open and closed mouth position. The lateral pole of each condyle was palpated anterior to the tragus of the ear and over the TMJ, and the posterior aspect of each condyle via the external acoustical meatus. Palpation pressure was firm (2 to 4 pounds) and was adjusted to the vulnerable patients, when appropriate.[20,22,23]

All pain reports of the participants during examination were recorded on a 5-point Likert scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

Echo intensity imaging of the digastric and geniohyoid muscles

In the patient group, QMUS was used to measure echo intensity of the digastric and geniohyoid muscles.[11] These two muscles were selected because of their anatomical location. The diagnostic value of muscle ultrasound and the test–retest reproducibility for the digastric muscle and the geniohyoid muscles was good.[11]

The region of interest was quantified by grey-scale analysis and calculation of z-scores (i.e. the amount of standard deviations below or above the mean of norm values); a reliable method with which changes in muscle architecture are assessed and compared with normal values.[24,25] The gray value of the mean of the left and right digastrics muscles and of the left and right geniohyoid muscle was expressed as z-scores. Z-score of < -2 and > 2 is considered abnormal. QMUS of the digastric and geniohyoid muscles proved to be feasible in healthy children and young adults, and is used for detection of structural changes in these muscles.[14]

Medical information and general physical abilities

In the patient group, information was gathered, among others, on body height, and baseline physical abilities were assessed by a physical therapist with expertise in pediatrics using a selection of MFM items. The MFM items have been previously been described.[15] The items 13 to 23 used in this study collect information about the sitting position, arm function, and

neck and head control. The MFM items were scored on a four-point Likert scale and summed to comprise a total raw score (range 0–33), in which the maximum represents normal motor function.

Based on the ambulatory function and the MFM, the patients were divided in early and late ambulatory stage (AS), early non-ambulatory stage (able to maintain posture) (ENAS), or late non-ambulatory stage (upper limb function and postural maintenance is increasingly limited) (LNAS).[26]

Statistical analysis

IBM SPSS version 20 was used to analyse the collected data. Mean and standard deviation were used to describe the average maximum mouth opening, the lateral excursions and the protrusion of the mandible in the patient and in control group. Paired Student's t-test was used to compare between-group continuous variable outcomes, and for dichotomous variables the chi-square test was used.

Patient data were further analysed using the 3 DMD stages. To compare test outcomes between the DMD stages ANOVA was used for scale variables and chi-square test for dichotomous variables.

Univariate and multivariate regression analyses were performed to determine which factors possibly affect the aMMO within the patient group (dependent variable). The independent variables were age, body height, MFM total scores, MFM score item 13-14, ultrasound score of the digastric muscle and geniohyoid muscle.

Results

Participants: Twenty-four patients with DMD were approached for inclusion in the study. One of the patients was excluded from the study because DMD was not genetically confirmed, and the signs and symptoms did not fit into the diagnosis DMD. For analysis the data of 23 patients and 23 age-matched males was used (Table 6.1). Patient characteristics of the total DMD sample as well as of the three stage groups are indicated in Table 6.2.

Table 6.1. Group comparison and descriptive statistics of the mandibular range of motion during clinical examination in the patient group (n = 23) and in the control group (n = 23). Mean and standard deviation of the measurements are referred to as $\bar{x}$ (SD).

Variables	Patient group n=23	Control group n=23	P-value
Mean age, yrs.mo (SD)	16.7 (7.7)	16.3 (6.7)	0.851
range	6.3 – 38.1	6.1 – 30.2	
aMMO[a] (mm) (SD)	43.5 (11.0)	54.6 (6.2)	< 0.0001*
range	21.0 – 59.0	40.0 – 63.0	
pMMO[b] (mm) (SD)	44.3 (11.1)	55.4(6.8)	< 0.0001*
range	21.0 – 62.0	40.0 – 68.0	
Lateral ROM L/R[c] (mm) (SD)	6.4 (3.0)	9.3 (1.7)	< 0.0001*
range	0.0 – 13.0	5.0 – 12.0	
Protrusion[d] (mm) (SD)	4.7 (3.5)	9.3 (2.5)	< 0.0001*
range	7.0 – 10.0	4.0 – 15.0	

* = Statistically significant differences.

[a]aMMO: active maximum mouth opening, the maximum interincisal distance on opening as wide as possible plus the vertical overbite (limited aMMO < 40mm).

[b]pMMO: passive maximum mouth opening, the maximum interincisal distance on active opening, with a slight overpressure on the edges of the upper and lower front teeth by the examiner plus the vertical overbite.

[c]Lateral ROM L/R: active mandibular lateral excursion, mean value between the left and right side.

[d]Protrusion: active forward movement of the mandible.

Questionnaire

A limitation in the ability to open the mouth was noted in 3 patients (13%) and pain during opening the mouth was mentioned in 4 other patients (17.4%, Table 6.2). The maximum intensity of the recorded pain in these 4 patients was ‘mild’.

Clinical examination of the masticatory system

In 6 patients (26.1%) mild pain could be provoked during aMMO, pMMO, or palpation of the masseter muscle, temporalis muscle or the lateral pole of the TMJ. Four of these 6 patients belonged to the LNAS (Table 6.2).

Table 6.2. Characteristics of patients with Duchenne muscular dystrophy (n = 23) presented by stages. Mean and standard deviation of the measurements referred to as $\bar{x}$ (SD) or number of patient as n / %. Statistically significant difference between the DMD stages, tested with ANOVA for scale variables and with chi-square test for dichotomous outcome. The significance in the dichotomous outcomes relates to the variable being absent or present.

Variable	Total (n=23)	DMD stage AS (1) (n=6)	ENAS (2) (n=7)	LNAS (3) (n=10)	p-value 1-2	2-3	1-3
Age, yrs.mo (SD)	16.7 (7.7)	8.4 (1.5)	15.0 (4.1)	22.8 (6.5)	0.004*	0.014*	<0.001*
range	6.3 – 38.1	6.3 – 10.5	10.7 – 20.6	16.3 – 38.1			
MFM, total raw score[a] (SD)	20.1 (12.6)	32.5 (0.8)	26.9 (8.3)	7.9 (1.4)	0.123	<0.001*	<0.001*
range	0 – 33	31 – 33	10 – 33	0 – 25			
MFM item 13-14[b] (SD)	3.7 (2.5)	6.0 (0)	5.4 (1.0)	1.2 (1.4)	0.172	<0.001*	<0.001*
range	0 – 6	6 – 6	4 – 6	0 – 4			
aMMO(mm)	43.5 (11.0)	47.5 (7.9)	49.1 (9.2)	37.2 (11.1)	0.739	0.034*	0.068
range	21 – 62	40 – 62	34 – 59	21 – 55			
pMMO (mm) (SD)	44.3 (11.1)	48.3 (7.6)	50.1 (9.5)	37.8 (11.1)	0.717	0.031*	0.060
range	21 – 62	42 – 62	34 – 60	21 – 55			
Lateral ROM L/R (mm) (SD)	6.4 (3.0)	7.3 (3.3)	8.2 (1.9)	4.7 (2.7)	0.556	0.009*	0.097
range	0.0 – 13.0	4.5 – 13.0	6.5 – 10.0	0 – 7.5			
Protrusion (mm) (SD)	4.7 (3.5)	7.0 (1.8)	4.9 (0.4)	3.2 (4.7	0.032*	0.296	0.082
range	7.0 – 10.0	5 – 10	4 – 5	-7 – 6			
EI digastric m., mean L/R[c] (SD)	2.0 (3.1)	0.5 (1.4)	1.3 (2.5)	3.4 (3.8)	0.517	0.221	0.052
range (z-score)	-1.3 – 10.6	-1.3 – 2.3	-0.8 – 6.1	0.6 – 10.6			
EI geniohyoid (SD)	6.0 (5.2)	2.4 (3.0)	5.6 (5.2)	8.3 (5.3)	0.209	0.297	0.024*
range m[c] (z-score)	-1.0 – 19.7	-0.10 – 8.0	1.5 – 15.3	0.6 – 19.7			
Body height (cm) (SD)	158.7 (21.9)	130.8 (8.8)	160.4 (16.0)	174.3 (12.8)	0.003*	0.083	<0.001*
range	120 – 195	120 – 146	131– 180	155 – 195			
MMO reduced, subj[d]	3 / 13%	1 / 17%	0 / 0%	2 / 20%	0.585		
Reduced TMJ sliding[e]	1 / 4%	0 / 0%	0 / 0%	1 / 10%	1.000		
Pain provocation[f]	6 / 26%	1 / 17%	1 / 14%	4 / 40%	0.491		

* = Statistically significant differences; DMD = Duchenne muscular dystrophy; AS = Early and late ambulatory stage; ENAS = Early non-ambulatory stage; LNAS = Late non-ambulatory stage.

[a]MFM: Motor Function Measure, domain 2, items 13 to 23 assessed axial en proximal motor capacities –12 items (total raw score 33 points); MFM score per item: 0 = does not initiate movement or starting position cannot be maintained; 1 = partially completes the exercise; 2 = completes the exercise with compensations, slowness or obvious clumsiness; 3 = completes the exercise with a standard pattern.

[b]MFM item 13-14: item 13: Seated on the chair without support of upper limbs or leaning against the back of the chair, maintains the sitting position, head and trunk in the axis; score 0 – 3; item14: Seated on the chair or in

their wheelchair. Head in flexion: from the fully flexed position, raises the head and maintains the raised position, head in the axis during the movement and when maintained; score 0 – 3.

[c]EI digastric L/R and geniohyoid muscles: echo intensity gray value (z-score) of the mean value of the left and right digastrics muscle and of the geniohyoid muscle; z-score < -2 and > 2 is abnormal.

[d]MMO reduced, subjective: limitation in the ability to open the mouth noted by the patients in Screen or by anamnestic information.

[e]Sliding of the temporomandibular joint was assessed by palpation: reduced = no or hardly any sliding of the lateral pole of the mandibular condyle, normal = sliding to and beyond the crest of the articular eminence.

[f]Pain provocation during active mouth opening, passive mouth opening, or palpation of the masseter muscle, temporalis muscle or the lateral pole of the TMJ.

Active and passive maximum mouth opening, active mandibular lateral ROM and protrusion were significantly smaller in the patient group than in the control group (Table 6.1). In the patient group, 6 (26%) had a reduced aMMO (< 40 mm). The difference between the aMMO and the pMMO in the patient and the control group was 1mm. The LNAS had a statistically significant smaller aMMO than the ENAS (Table 6.2).

The active mandibular lateral ROM was reduced (< 8 mm) in 16 patients (70%); all patients in the LNAS had a reduced lateral ROM. The LNAS had a statistically significant smaller lateral ROM than the ENAS (Table 6.2).

The active mandibular protrusion was reduced (< 5 mm) in 7 patients (30%). The ENAS had a statistically significant smaller protrusion than the AS (Table 6.2).

Clinical examination of the mobility of the temporomandibular joint revealed that 22 patients (96.0%) had a normal sliding of the mandibular condyle (Table 6.2). All controls had normal sliding of the mandibular condyle.

Echo intensity imaging: The echo intensity of the anterior belly of the digastric muscles, expressed as z-score, was found to be increased (z > 2) in 16.6% of the patients in the AS, 28.6% in ENAS and 50.0% in LNAS. The echo intensity of the geniohyoid muscles was increased in 50.0 % of the patients in AS, 85% in ENAS and 90.0% in LNAS. There was a statistically significant difference between the AS and LNAS regarding the echo intensity of the geniohyoid muscles (Table 6.2).

General physical abilities: There was a significant difference in the MFM score between the ENAS and LNAS, and between AS and LNAS regarding the MFM total score (Table 6.2).

There was a statistically significant difference between the ENAS and LNAS, and between AS and LNAS regarding the MFM items 13-14 score.

Predictive factors for the active maximum mouth opening:

Univariate linear regression analysis outcomes of potential determinants of aMMO in patients with DMD are presented in Table 6.3. The univariate linear regression analysis revealed negative correlations between the aMMO and age, body height, ultrasound score of the digastric muscle and geniohyoid muscle, and positive correlations for the MFM variables. Because of the small number of patients only two variables are used in our multiple linear regression analysis. Age and MFM variables are strongly correlated (Pearson correlation 0.828; $p < 0.001$) via disease progression, making age less informative. Therefore we entered body height in the model which in combination with MFM total raw score improved the model ($R^2 = 0.71$).

Table 6.3. Univariate linear regression analysis of determinants of the impaired active maximal mouth opening (aMMO) in Duchenne muscular dystrophy patients.

		95 % Confidence Interval for Effect			
Variable	Effect	Lower Bound	Upper Bound	p-value	R^2
Age (in years)	-0.52	-1.35	0.28	0.005*	0.13
Body height (cm)	-0.12	-0.33	0.10	0.270	0.06
MFM total raw score	0.64	0.39	0.90	<0.001*	0.57
MFM item 13-14	2.65	1.06	4.23	0.002*	0.37
EI digastric muscle (z-score)	-1.67	-3.07	-0.27	0.022*	0.23
EI geniohyoid muscle (z-score)	-0.99	-1.84	-0.14	0.024*	0.22

* = Statistically significant differences.

Table 6.4. Multiple linear regression analysis of determinants of the impaired active maximal mouth opening (aMMO) in Duchenne muscular dystrophy patients

		95 % Confidence Interval for Effect		
Variable	Effect	Lower Bound	Upper Bound	p-value
(Constant)	-14.360	-45.550	16.831	0.348
Body height (cm)	0.247	0.078	0.415	0.006*
MFM total raw score	0.932	0.639	1.225	<0.001*

R^2 = 0.71; * = Statistically significant differences.

Discussion

In this study the impact of DMD on the mandibular movements was assessed by comparing the mandibular ROM of patients with those of a gender and age matched healthy control group. Also, mandibular ROM per ambulatory stage (AS, ENAS or LNAS) in the DMD group was examined. Predictive factors were established for reduced aMMO in the patient group. This study shows that mandibular ROM was significantly lower in patients with DMD compared to controls. The decreased aMMO in patients with DMD was primarily related to body height and higher disease severity, expressed by the motor function.

Measurement of the mandibular movements is a standard procedure for evaluation of the musculoskeletal masticatory structures.[18,22] As an entity on itself the aMMO is a parameter that can be established reliably, regardless of the severity of the limitation; the interobserver intraclass correlation coefficient (ICC) was 0.98 and the intra-observer ICC and intersession ICC reliabilities both were 0.99.[27]

In view of the wide range of variation of individual mandibular movements, it is difficult to set normal ranges and uniformity regarding the maximum movements. Suggested cut-off values for the aMMO in healthy subjects vary between 40–44 mm for man, 38–42 mm for woman and 35–40 for children.[28-33] In accordance with the literature, we consider for our study < 40 mm for aMMO, < 8 mm for active lateral excursion and < 5 mm for protrusion as reduced. These values do not seem to be in conflict with other findings from the literature.

In our study we have incorporated the concept of the mandibular range of motion as an anatomical position (condyle in relation to the crest of the eminence next to the interincisal measurement of mandibular movements).[34] Healthy individuals may perform normal opening

with highly variable amounts of condylar translation, and variation in maximum incisor opening is largely explained by variation in the amount of mandibular rotation.[37] It is mentioned in the literature that maximum incisor opening does not provide reliable information about condylar translation and its use as a diagnostic indicator of condylar movement is limited.[35] A combination of the interincisal measurement of mandibular opening and assessment of the anatomical condylar position in relation to the crest of the eminence will improve establishing whether the impairment is intra-articular or not.[34]

Regarding aMMO in patients with DMD compared to healthy controls, conflicting objective data can be found in the literature ranging from a reduced aMMO to a non-significant difference.[3,4] The mean reduction of the aMMO of our patient group compared to the age and gender matched controls was 11 mm, which is a clinically relevant difference. In another study, aMMOs of 39.1 mm (DMD patients, mean age 11.7 years) and 54.2 (healthy controls, mean age 11.9 years) were found.[4] However, in a Japanese population, no significant difference between the DMD group and the control group was found, although the aMMO of the patients tended to be less compared to controls (mean age 21.5 vs. 21.3, aMMO 36.9 vs. 41.0 mm).[3] Despite the higher mean age in the latter study the aMMO was less than reported in the study of Botteron et al. (2009) and our study.[4] All studies included the vertical overbite in their measurements. Differences in ethnicity and instructions during the examination of the studied population in these studies may explain the variation of the aMMO values.

The mandibular ROM is influenced by many factors, i.e. age, gender, body height, ethnicity, status of the masticatory system, cervical column function, and head and neck posture.[32, 36, 37] In patients with DMD, sonography indicated fatty infiltration related to the dystrophic changes of the masseter muscle and the suprahyoid muscles.[4,11] Muscle dystrophy may lead to muscle stiffness and consequently may hamper mouth opening and horizontal jaw movements. In our study, 5 out of 6 patients with a limited aMMO (< 40 mm) had a normal sliding of the condyle indicating that structural changes in the muscles may primarily be responsible for the reduced mandibular ROM in general and the aMMO specifically.

The differences between patients and controls regarding the mandibular ROM and not only maximum mouth opening indicates a more general muscle involvement than the muscles responsible for mouth opening and closing. The lateral pterygoid muscles play an important role in mouth opening but also in the control of horizontal mandibular movements such as protrusion and lateral ROM.[38] In patients with spinal muscular atrophy involvement of the lateral pterygoid muscle was found to play an important role in the impairment of the

mandibular movement in this type of neuromuscular disorder.[41] To our knowledge, the effect of DMD on the lateral pterygoid muscle is not investigated by MRI.

In healthy individuals, the strength of the vertical component of the mouth opening muscle force (suprahyoid and indirectly the infra-hyoid muscles) is important in mouth opening.[40] The structural changes found in the anterior belly of the digastric muscles and geniohyoid muscles in DMD may lead to a decreased strength and contribute to a reduced aMMO. Our linear regression analysis confirms this hypothesis: the echo intensity of the digastrics and geniohyoid muscle correlated with the maximum mouth opening (Table 6.3). Moreover, the quantitative muscle ultrasound imaging in the patient group showed that the muscle echo intensity of the suprahyoid muscles increased gradually (z-sore > 2) with ambulatory loss.[11] The influence of DMD on the suprahyoid (and probably the lateral pterygoid) muscles in our patients seems to follow a tendency like other physical characteristics that start to develop according to the stage of the disease.

The study of L van de Engel-Hoek et al. (2012) showed the feasibility of quantitative muscle ultrasound of digastric muscles, the geniohyoid muscles in healthy subjects and patients with DMD.[11] QMUS showed significant differences in echo intensity between healthy subjects and DMD patients, especially in the geniohyoid muscle. The anatomic location and structure of e.g. the mylohyoid muscle proved to be too thin to be measured and analyzed. However, we do not expect that other oral muscles such as the mylohoid muscles are spared from DMD.

In this cohort of 23 boys and adults with DMD, the linear regression analysis revealed the severity of DMD, assessed by the MFM, and the height of the patient, to be the strongest independent predictive factors for a reduced aMMO (Table 6.4). Although age and height are generally related, in patients with DMD, due to the growth disturbances, height turned out to be a stronger independent factor for a reduced aMMO than age (Table 6.4).

A reduced mouth opening may hamper feeding, oral hygiene and dental care. Recognizing this impairment and their predictive factors by medical staff, patients, parents and caretakers is a first step. Furthermore, in terms of management, it is important to take measures to slow down the development of the mouth opening reduction, possibly by developing a training program. The program has to be easy to implement in daily life and with low intensity aerobic exercises as suggested in other training programs for patients with DMD.[41,42]

Conclusion

Mandibular movements in DMD are significantly reduced compared to the healthy controls, and become more hampered with loss of motor function, including the sitting position, arm function, and the neck and head control. We suggest that evaluation of the aMMO as an expression of the reduced mandibular range of motion becomes a part of routine care of patients with DMD.

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Chapter 7

Fighting against disuse of the masticatory system in Duchenne Muscular Dystrophy: a pilot study using chewing gum

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Abstract

Objectives: Duchenne muscular dystrophy (DMD) patients report masticatory problems. The aim was to determine the efficacy of mastication training in DMD using chewing gum for 4 weeks.

Methods: 17 patients and 17 healthy age-matched males participated. The masticatory performance was assessed using a mixing ability test and measuring anterior bite force before, shortly after and one month after the training.

Results: In the patient group the masticatory performance improved and remained after one-month follow-up, no significant changes in anterior maximum bite force was observed after mastication training. In the healthy subject the bite force increased and remained at the one month follow-up; no significant difference in masticatory performance was observed.

Conclusions: Mastication training by using sugar free chewing gum in DMD patients improved their masticatory performance. Since bite force did not improve, the working mechanism of the improvement in chewing may relate to changes of the neuromuscular function and coordination, resulting in improvement of skills in performing mastication.

Introduction

Duchenne muscular dystrophy (DMD) is an inherited, progressive disorder due to mutation in the dystrophin gene. This leads to shortage or absence of dystrophin which results in generalized degenerative weakness and muscle wasting.[1,2] Previous studies mention that the proximal muscles of the extremities are affected first.[3] However, in the literature it has been suggested that the orofacial and masticatory musculature might be affected earlier in the disease process than expected, indicated by the presence of dental abnormalities and structural changes in the tongue prior to a reduction of the motor function of the upper part of the body.[4, 5]

Feeding, chewing and swallowing difficulties have been reported in the advanced stages of DMD. [6,7] The reported masticatory difficulties (e.g. biting of food and eating hard and sticky food) may be caused by masticatory muscle involvement in both ambulant and non-ambulant DMD patients.[8,9] The increasing mastication difficulties in combination with progressive oropharyngeal and hyolaryngeal weakness will contribute to weak pharyngeal clearance and consequently to progressive dysphagia in advanced stages of DMD.[7] Reduced bite force and reduced contacts between the upper and lower (pre) molars in patients with DMD compared with healthy subjects, are partly responsible for the mastication difficulties including less fragmentation of food.[5,10,11] Poor fragmentation of food in combination with weak pharyngeal clearance may increase pharyngeal post swallow residue and may cause in advanced stages of DMD swallowing difficulties like choking and the feeling of sticking food in the throat.[4] Problems with feeding, including e.g. prolonged feeding times, can have a psychological impact like embarrassment and social isolation and this adversely affects quality of life.[9,12] As a consequence patients may try to avoid prolonged feeding times, which may lead to inadequate nutrition and may increase the rate of disease progression.[13-15] When weight loss becomes a health issue for the non-ambulatory DMD patients, food adaptation (soft or chopped food) has to take place mainly to ensure sufficient calorie intake.[9,16] In healthy individuals a softer diet is associated with a reduced bite force which influences negatively the chewing efficiency.[17] We expect that the food adaptation in our patient group will have a similar effect on the masticatory system. Therefore, keeping the masticatory system active may delay, stabilize or improve masticatory function in DMD.[5] Before starting a disease-specific training program, it is important to know the dominant limitation and the underlying mechanisms of this limitation. A recent study reported that impairment of the masticatory system, expressed as decreased masticatory performance, was common among boys and men with DMD and was primarily related to higher disease

severity. In that cohort of DMD patients the masticatory performance was moreover correlated, albeit weakly, with the bite force which may offer possibilities for intervention, as it is a possible modifiable factor.[5] In this pilot study we therefore focused on the effect of a masticatory low intensity aerobic exercise using chewing gum upon the bite force and the masticatory performance.

A previous study indicated that low intensity aerobic exercise of the legs and arms can stabilize functional performance in ambulant and wheelchair-dependent boys with DMD.[18] To our knowledge low intensity aerobic training of the masticatoy system fitting in daily life routine in patients with DMD has not been described. In healthy subjects, the bite force, which is related to masticatory performance, was increased through exercise of the masticatory system. [19-21]

This study aims to assess the efficacy of training the masticatory muscles using sugar free chewing gum in patients with DMD.

Methods

Participants

Twenty-three boys and adult men with DMD originating from the cohort of the swallowing study of van den Engel-Hoek et al. (2013) were asked to participate in the training study.[4] Seven of the 23 patients were not able to participate due to the following reasons: 1 patient was excluded because DMD was not genetically confirmed, and the signs and symptoms did not fit into the DMD diagnosis, 2 patients were afraid of food aspiration, 1 patient due to time restriction (moving), and 3 patients preferred not to take part without mentioning any reason. Seventeen patients and 17 age-matched healthy males participated in the training between May 2010 and February 2012.

The patients were recruited through announcements by patient organizations. In younger DMD patients genetic information was available, however in older patients this was not the case. In these patients the clinical course of the disease was evaluated and compared to data of natural course and the criteria of Emery (1991).[22] Based on the latter, when patients had a Duchenne phenotype and Becker phenotype they were excluded. Patients who were totally dependent on tube feeding were excluded. Healthy subjects up to the age of 18 years were recruited at a primary and secondary school located in the western part of the Netherlands, those above 18 years were recruited among the students of the College of Dental Sciences, Nijmegen, the Netherlands. Exclusion criteria for the healthy subject were: a history of neuromuscular disease, signs and symptoms of temporomandibular disorders, orthodontic

treatment or morphologic dental malocclusions. Age limits in the study were set above 5 years of age to ensure cooperation of the participants during the study. Exclusion criteria for the participants were a daily chewing gum habit, or gum chewing for more than 30 min. per week. Eligible participants and their guardians received a letter with an invitation to participate in the study. Written informed consent was obtained from all participants and if needed the guardians of the participants.

Protocol

In this pilot study, the patients and healthy subjects were examined at base line (T_0), after four weeks mastication training (T_1), and at 1-month follow-up (T_2). All participants underwent a clinical examination of the masticatory system, measurement of the anterior maximum voluntary bite force (MVBF) and the mixing ability at T_0, T_1 and T_2. At T_0 the patients underwent an assessment of their physical abilities using the Motor Function Measure (MFM). The main outcome measures to determine the efficacy of the mastication training were bite force and masticatory performance (mixing ability). The participants were not aware of the outcome parameters of the mastication training. Possible negative side effects of the mastication training were evaluated by means of the clinical examination of the masticatory system including assessment of the mandibular range of motion and pain on palpation of the masticatory muscles and temporomandibular joints.

Clinical examination of the masticatory system

All participants in this study were clinically examined following the validated procedure as described by Lobbezoo-Scholte et al. (1993, 1994).[23, 24] This clinical examination included measurement of the mandibular range of motion (ROM), palpation of the masticatory muscles and the temporomandibular joints. All pain reports during examination were recorded on a 5-point Likert scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. The number of occlusal contacts (OC-score) between the premolar and molar teeth of the upper and lower jaw, after the teeth were brought into occlusion, were assessed using wax records (Moyco beauty pink plate wax). A perforation in the wax record indicated an occlusal contact. Unilaterally, the maximum OC-score is 5 (1 OC per posterior occluding pair); bilaterally the maximum is 10.

Measurement of the anterior maximum voluntary bite force

The VU University Bite Force Gauge (VU-BFG) is a handheld device which uses a load cell (LPM 510 250lb) to MVBF.[25] The strain gauge element was placed parallel with the Frankforter horizontal which is defined as the line between the lowest point on the margin of the orbit to the highest point on the margin of the auditory meatus. The gauge is placed between the upper and lower central incisors and midway between the central maxillary incisors. Patients and healthy subjects clenched as hard as possible for 3 seconds and repeated clenching three times with an interval of 30 seconds rest periods; the highest value of the three measurements was used.

Figure 7.1. Masticatory training box distributed to all participants. The box included six chewing gum packs, a stopwatch and a diary.

Mixing ability test

In all participants, masticatory performance was measured using the mixing ability test, described by Speksnijder et al. (2009).[26] A wax tablet, consisting of a red and a blue wax layer, was offered to the subjects (tablet at room temperature, 20 °C). The investigator (H.W.v.B.) instructed the participants as follows: chew on the tablet as if you are eating a piece of bread, I will give a signal to start and stop with chewing. Each participant performed 20 mastication strokes on the wax tablet, and as a result the colours would mix. The investigator counted 20 strokes without informing the participant in order to avoid influencing

of mastication process. The chewed tablet was assessed blinded and independently and cleaned for analysis. The chewed wax tablets are flattened and photographed from both sides with a high-quality scanner (Epson_ V750, Long Beach, CA, USA). The spread of the color intensities in the combined image of both sides is the measure of mixing. The images of the wax are processed using Adobe Photoshop, CS3 extended (Adobe, San Jose, CA, USA). The intensity distributions of the red and blue channels are exported as 8-bit histograms. The histograms of both sides of the wax are added to obtain the red and blue intensity distributions of the combined image of both sides of the flattened wax. These histograms are analyzed to obtain a measure for the mixing of the wax: the mixing index. The degree of mixing represented the masticatory performance. A low mixing index indicates a better masticatory performance than a high index.

Physical abilities

At baseline (T_0), medical information was gathered about ventilation support. The validated Motor Function Measure (MFM) scale, items 13 to 23, was used to evaluate the sitting position, function of the arms, neck and head control in the patient group.[27, 28]

Masticatory training

At the start of the masticatory training all participants received a box including six chewing gum packs, stopwatch and a diary (Figure 7.1). All participants followed the same program which was written on the back side of the box and on the chewing gum wrappers. All participants used the same brand chewing gum to guarantee the same toughness (Stimorol sugar free; Dandy As, Denmark). The instructions for the mastication training consisted of using one piece of chewing gum of 22 grams per exercise, 3 exercises of each 30 min per day, 5 days/week, over a period of 4 weeks. To increase compliance participants had two days rest per week. The participants kept a diary to check for compliance and potential complications.

Stratification of the patients

After removing 3 ambulatory patients from the data set a post hoc analysis was performed with 14 non-ambulatory patients. Based on the ambulatory function and the MFM, 14 patients were divided into two subgroups: early non-ambulatory stage (able to maintain posture) (ENAS, n = 7) and late non-ambulatory stage (upper limb function and postural maintenance is increasingly limited) (LNAS, n = 7).[14]

Statistical analysis

Student's t test for paired data was used to assess possible differences between measurements at T_0, T_1 or T_2 within each group of participants and in a post hoc analysis within 14 non-ambulatory patients. The level of significance was set at $p = 0.05$. All analyses were performed with IBM SPSS Statistics 20 software.

Student's t test for paired data was used to assess possible differences between measurements at T_0, T_1 or T_2.

Results

For analysis, the data of 17 patients with a mean age of 16.6 years (S.D. 6.1, range 7.4–28.1) and 17 healthy age-matched males with a mean age of 16.4 years (S.D. 6.0, range 6.1–30.2) were used. The characteristics of the participants at baseline are indicated in Table 7.1.

Clinical examination of the masticatory system

The OC score in the posterior teeth of the upper and lower jaw was reduced in more than 50% of the patients (average OC score 3.1, SD 2.0, range 0–7) compared with the healthy subjects (average OC score 6.9, SD 1.2, range 5–8).

In 4 patients (24%) mild pain could be provoked during the clinical examination: 1 patient during passive maximum mouth opening (pMMO) at T_0, 1 patient during pMMO at T_0 and T_1, 1 patients during pMMO at T_0, T_1 and T_2, and 1 patient during palpation of the masseter muscle and the lateral pole of the TMJ at T_0 and T_1.

Data of the mandibular ROM are indicated in Table 7.2. In the patient group, no significant differences could be demonstrated between measurements at T_0, T_1 or T_2 regarding the mandibular range of motion. In the healthy subjects, a significant difference could be demonstrated between measurements at T_1 or T_2 regarding the protrusion, albeit within the smallest detectable change of 2 mm (Table 7.2).[27]

Masticatory performance

Patients had a significant higher mixing index at T0 (less masticatory performance) than controls ($p < 0.001$), (Table 7.2). On an individual level the mixing index increased (more masticatory performance) in all patients, except one, after the mastication training (Table 7.1). The mixing ability of the patient group increased significantly after the mastication training. At the one-month follow-up the effect remained. In the healthy subjects, the mixing ability did not change significantly.

Table 7.1. Base line characteristics of patients with Duchenne muscular dystrophy (DMD, n = 14) to determine the efficacy of mastication training using chewing gum for 4 weeks

Patient no.	Age yrs. mths	DMD stage[a]	MFM score[b]	Age stop walking yrs. mths	Ventilatory support[c]	Prednisone use[d] Y/N	Mixing index		
							T_0	T_1	T_2
1	11.6	2	100	-	0	Y	21.1	21.4	19.5
2	13.2	2	93	12.0	1	Y	26.5	24.2	25.1
3	8.3	1	100	-	0	Y	28.3	20.9	22.0
4	10.8	2	100	-	0	Y	25.0	27.3	28.2
5	16.3	3	30	11.0	1	Y	27.8	23.6	23.9
6	12.0	2	96	-	0	Y	20.7	19.1	18.8
7	19.7	2	30	9.6	0	Y	21.5	21.2	23.6
8	17.2	3	33	10.0	1	N	30.2	24.6	25.9
9	20.8	3	27	11.0	1	N	29.7	24.7	25.4
10	22.3	3	0	8.0	2	N	29.1	28.4	28.0
11	28.3	3	21	11.0	1	N	26.6	23.8	23.7
12	24.8	3	0	9.0	2	N	27.0	26.7	24.9
13	7.4	1	100	-	0	Y	29.0	26.5	26.9
14	9.7	1	100	-	0	Y	17.2	16.4	18.0
15	17.4	2	72	10.0	0	N	21.1	16.6	18.3
16	20.6	2	75	13.0	0	N	22.2	18.1	16.1
17	21.8	3	75	12.0	0	N	24.2	23.4	25.6

[a]DMD stage: scored as 1 = ENAS = Early non-ambulatory stage; 2= LNAS = Late non-ambulatory stage.

[b]MFM: Motor Function Measure, domain 2, items 13 to 23 assessed axial en proximal motor capacities –12 items (total score 33 points = 100%); MFM score per item: 0 = does not initiate movement or starting position cannot be maintained; 1 = partially completes the exercise; 2 = completes the exercise with compensations, slowness or obvious clumsiness; 3 = completes the exercise with a standard pattern.

[c]Ventilatory support: scored as 0 = none; 1= part-time (nocturnal); 2 = continuous noninvasive; 3 = continuous + tracheostomy.

[d]Prednisone: % of patients using prednisone at base line or previously.

Table 7.2. Means and standard deviations of mixing ability, bite force (front) and active maximum mouth opening (aMMO) for patients (n = 17) and healthy subjects (n = 17) at the three measurement moments: T_0, before exercise; T_1, after 4 weeks of exercise; T_2, 4 weeks after last exercise. Pat: patients; H: healthy controls. P-values are given of the differences between measurement moments (T_0-T_1, T_0-T_2 and T_1-T_2). Abbreviations: Δ, difference between measurement moments; CI, confidence interval.

		T_0	T_1	T_2	$T_0 - T_1$		$T_0 - T_2$		$T_1 - T_2$	
		$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	Δ (95% CI)	P	Δ (95% CI)	P	Δ (95% CI)	P
Mixing ability[a]	Pat	25.1 (3.9)	22.8 (3.7)	23.2 (3.7)	2.37 (1.09...3.65)	0.001	1.96 (-1.11...0.29)	0.008	-0.41 (0.58...3.34)	0.23
	H	17.3 (2.8)	17.6 (2.4)	17.6 (2.3)	-0.23 (-1.8...1.35)	0.76	-0.29 (-1.65...1.07)	0.66	-0.06 (-1.28...1.16)	0.92
Anterior MVBF[b] (N)	Pat	97 (33)	99 (48)	98 (41)	-2.26 (19.71...13.90)	0.79	1.08 (-14.81...16.87)	0.89	5.30 (-9.52...20.11)	0.46
	H	170 (89)	207 (71)	214 (110)	-35.61 (57.68...-13.44)	0.004	-42.48 (-78.77...-6.08)	0.025	-6.87 (-44.24...30.51)	0.70
aMMO[c] (mm)	Pat	44.7 (9.9)	44.1 (9.8)	44.2 (9.9)	0.53 (-0.53...1.59)	0.31	0.41 (-0.87...1.7)	0.51	-0.12 (-1.39...1.15)	0.85
	H	55.7 (6.3)	55.9 (6.0)	56.4 (6.1)	-0.24 (-1.85...1.38)	0.76	-0.65 (-2.02...0.72)	0.33	-0.41(-1.3...0.48)	0.34
Lateral ROM L/R[d] (mm)	Pat	6.7 (2.2)	6.6 (1.9)	6.9 (1.9)	0.18 (-.45...0.81)	0.56	-0.15 (-0.78...0.49)	0.63	-0.32 (-0.7...0.05)	0.09
	H	9.2 (1.9)	10.0 (1.0)	9.7 (1.6)	-0.79 (-1.28...-0.3)	0.003	-0.5 (-1.26...0.26)	0.18	0.29 (-0.53...1.12)	0.46
Protrusion[e] (mm)	Pat	5.1 (2.1)	5.5 (1.6)	5.3 (2.0)	-0.41 (-1.62...0.79)	0.48	-0.18 (-1.05...0.7)	0.67	0.24 (-0.63...1.1)	0.57
	H	9.5 (2.5)	9.2 (1.7)	9.9 (2.3)	0.35 (-0.67...1.38)	0.48	-0.35 (-1.2...0.5)	0.39	-0.71 (-1.38...-0.03)	0.041

[a]Mixing ability: individual's capacity to grind a two colored wax tablet during 20 strokes of mastication. A low mixing index indicates a better masticatory performance than a high index.

[b]Anterior MVBF: maximum vertical interocclusal bite forces between the central incisors of the upper and lower jaw anterior maximum voluntary bite force in Newton.

[c]aMMO: active maximum mouth opening, the maximum interincisal distance on opening as wide as possible corrected for the vertical over bite (limited aMMO < 40mm).

[d]Lateral ROM L/R: active mandibular lateral excursion, mean value between the left and right side.

[e]Protrusion: active forward movement of the mandible.

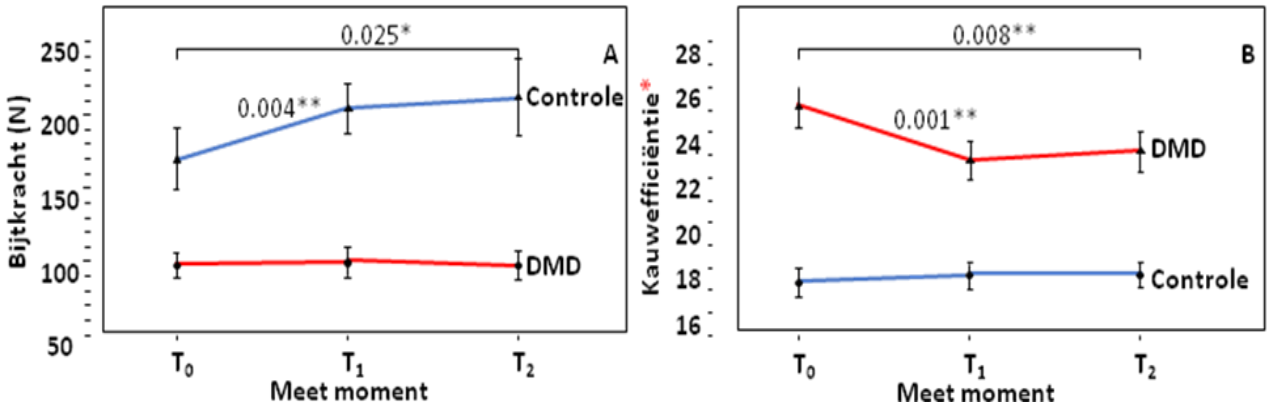

Figure 7.2. The effect of mastication training expressed by mixing ability and bite force using chewing gum in patients with DMD. (A) masticatory performance expressed as mixing ability, and (B) bite force (in N) at base line (T_0), afer four weeks mastication training (T_1), and at 1-month follow-up (T_2) for the patients with DMD and the healthy subjects.

Anterior Maximum Voluntary Bite Force

Patients had a significant lower MVBF than controls at T_0 ($p = 0.001$), (Table 7.2 and Figure 7.2 B). MVBF in the patient group did not change, whereas in healthy subjects a significant increase after the mastication training was observed at T_1. After the 1-month follow-up this effect remained (Figure 7.2 B).

Age effect

Scatter plots were used to scan for the presence of age specific effects of the masticatory training. This was done for mixing ability, anterior MVBF, aMMO, lateral ROM L/R and protrusion. For all of these outcomes age specific effects were not seen.

Compliance and side effects

All participants started the training followed the 4-week program according to the instructions. Analysis of the diaries of the patient group and healthy subjects showed that the compliance was high; in the patient group an average of 94% and in the healthy subjects an average of 99% of the required hours of training.

During T_1 and T_2 no serious adverse events were observed or reported in the questionnaires. One 12 year old patient had to reduce the intensity of the training in the second week because of catching flu. Another, 24 year old, patients with non-invasive ventilatory support mentioned temporomandibular pain symptoms during the T_1 examination. One healthy subject developed headache after the training session during the second day of training which diminished after a few minutes. Other participants did not indicate any other side effects in terms of pain, fatigue in the masticatory system, choking chewing gum nor were other unexpected effects reported.

Post hoc analysis

The mixing ability of the 14 non-ambulatory patients increased significantly after the mastication training. At the one-month follow-up the effect remained. MVBF in the 14 non-ambulatory patients did not change.

Discussion

The present study investigated the efficacy of mastication training in patients with DMD by assessing the MVBF and the masticatory performance. Mastication training significantly improved the mixing ability in patients with DMD whereas their MVBF did not change.

Eating is a social activity and plays an important role in nutrition intake and health. Eating is disturbed by progressive dysphagia in the advanced stages of DMD.[4] Poor mastication of food in combination with weak pharyngeal clearance may increase pharyngeal post swallow residue and choking. [8,30] If masticatory performance is trainable this may have a positive effect on pharyngeal residue and choking.

Previous studies in healthy individuals demonstrated an increase of the bite force after masticatory training using chewing gum.[19,20] In these studies, hard chewing gum was used. Such hard gum can, however, be too hard to chew upon by patients with DMD. Therefore, in our study we used a softer type in order to make the training for the patients feasible. The training, modified for gum hardness as well as for duration and frequency, was tested also in

healthy subjects. Despite the differences in training compared to previous studies, our healthy subjects demonstrated an increase of MVBF as well, indicating the efficacy of our training program. The improvement of the masticatory performance in our patient group was significant, although they did not reach the level of the healthy controls (Figure 7.2 B). Their masticatory performance reached the level of patients wearing full dentures (mixing ability 21.2, SD 3.6). Keeping in mind the small numbers in this pilot study, in the post hoc analysis there was no difference in efficacy of the training between the early and late non-ambulatory patient group. Since OC and MVBF did not change after the training period, it is striking to observe an improvement of the masticatory performance. The skill to move the chewing gum around the mouth and keeping it between the teeth was trained for 4 weeks. Chewing the wax tablet is very much alike. Therefore the improvement of masticatory performance in the DMD group after mastication training may be caused by improvement of motor control and coordination resulting in an improvement of skills in performing mastication as the specific task rather than by changes of the masticatory muscle force. The study of Jansen et al. described a similar phenomenon when bicycle training for the extremities was applied in DMD.[18]

The study of Kawazoe et al. regarding training the masticatory system in patients with DMD does not fit the criteria suggested for exercise programs for patients with NMD.[31] As a part of that training program the patients had to clench the jaws as hard as possible for 5 minutes which is not a low intensity aerobic exercise. Moreover, clenching the jaws may be too difficult to perform for DMD patients because of the early loss of MVBF and the loss of posterior occlusal contacts between the jaws in a later stage of the disease. The study of Nozaki et al. describes a range of motion exercise and demonstrates a significant increase of the occlusal force and the patients' satisfaction with meals.[32] Both training methods cannot be performed by the patient himself and are difficult to fit into daily life routine.

Training of masticatory muscles by using chewing gum fits the criteria suggested for exercise programs in DMD; the training is safe, low in intensity, rhythmic, continuous, and aerobic, fits in the daily life routine and can start at a young age.[33-35] The compliance of the patient group and healthy subjects was high. Moreover, sugar free chewing gum contains polyols which are alcohol derivates of sugar. Polyols improve oral health by stimulating salivary flow, which results in an increased buffering capacity after sugar intake.[36] The polyol xylitol in the chewing gum used in this study reduces the amount of Streptococcus mutans, which plays an important role in the development of the amount of caries inducing bacteria.[37]

If mastication training would cause negative side effects, development of signs and symptoms of temporomandibular dysfunction (TMD) during or after the training would be expected. The main signs and symptoms of TMD, e.g. reduced mandibular ROM, mandibular deviation on opening, pain on palpation of the masticatory muscles and temporomandibular joint, did not occur throughout the training except in one patient. This 24 year old patient with non-invasive ventilatory support mentioned TMD symptoms during the T_1 examination. After instructing how to adjust the air tube, the pain symptoms disappeared at T_2. We may conclude that the pain symptoms in this patient were caused by the poorly positioned air tube. In the 3 patients we could provoke pain during the clinical examination by opening the mouth passively. We suggest that this can be attributed to contracture of the masseter muscle rather than to TMD symptomatology. The patient who catched flu consulted the investigator and started training again in the second week after 3 days rest. In the healthy subject with headache after the training session, the headache diminished already after a few minutes.

The following limitations within this study have to be taken into account. First, ideally a group of patients would be randomized and controlled, e.g. training vs. no training would be contrasted. In orphan diseases, such a study design is not or hardly feasible. Since we designed our study as a pilot, in future studies a baseline measurement 4-6 weeks before the training starts would give more strength to the results. Second, the wax tablets may have been too tough for mixing by patients with DMD. It is suggested to offer the wax tablet at a higher temperature in patients with severely compromised masticatoy performance.[25] Prior to the start of the study, we offered tablets at a temperature of 30 °C to three subjects. Under these conditions, pieces of wax were sticking to the teeth and a coherent bolus could not be collected which lead to the decision to offer the wax tablets at room temperature. Third, due to the small number of patients in our pilot study, it is not possible to state whether the mastication training is more effective in subgroups of patients stratified by age or motor function. We used scatter plots to establish age specific effects of the masticatory training on each of the variables masticatory performance, anterior MVBF, aMMO, lateral ROM L/R and protrusion. For all these outcomes age specific effects were absent. The post hoc analysis with 14 non-ambulatory patients showed the same results compared to the group of 17 DMD patients. Fourth, we cannot determine whether the increase in masticatoy performance in the patients with DMD was further influenced by exposure to prednisone. The post hoc analysis did not give additional information on this issue.

Changes in the masticatory system like dystrophic changes in submental muscles and the tongue, dental abnormalities and decrease of the MVBF and labial force are developing early in the disease process.[4,5,10] These changes lead to deterioration of the masticatory performance already in the ambulatory stage of DMD.[5] When dystrophic changes in the masticatory and the submental muscles are present, patients may be less responsive to the mastication training.[5,8] This may indicate that masticatory training has to start as early as possible. In the advanced stage when patients have to adjust to a soft diet because of health issues, e.g. insufficient food intake because of prolonged mealtime, mastication training can activate the masticatory system.[5] Mastication training may postpone the deterioration of the masticatory system and preserve functional skills.

To preserve functional skills of the mastication system we suggest patients with DMD to (1) treat the patient with DMD within a multidisciplinary setting to integrate stimulation of the masticatory system in a safe feeding plan (2) keep the masticatory system active by eating solid food as long as it is safe regarding health issues; the airway defense mechanisms, cough strength and calorie intake has to be sufficient (3) supplement eating by mastication training using sugar free chewing gum at the age of 6 and older when it is safe to use chewing gum; the child only chews and never swallows the gum (4) when adjustment to a soft diet has to take place because of health issues, continue the mastication training.

Future research is needed to investigate (1) if an increase of the duration (e.g. 16 weeks) of the training will increase its efficacy and (2) if patients in an early disease stage are more responsive to masticatory training compared to patients in a late disease stage.

Conclusion

Mastication training by using sugar free chewing gum in patients with DMD improved the masticatory performance. The working mechanism of this improvement was not related to an increase of the MVBF, but might be related to changes of motor control and coordination followed by improvement of skills in performing mastication as the specific task.
Future research is needed to assess the efficacy of masticatory training in a larger number of patients, ideally using a randomized controlled design.

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PART III

General discussion and Summary

Chapter 8

General discussion

Introduction

Medical care for patients with a neuromuscular disorder (NMD) has improved the quality of life and increased longevity.[1,2] However, the increased longevity has resulted in non-fatal medical complications of the disease, such as limitations in mandibular function, which become more prominent and require more attention. While the medical care for patients with NMD includes medical, surgical, and rehabilitation approaches an assessment of mandibular function is not yet included.

Impaired mandibular function, which is often reported by children and adults with NMD, is an important causal factor for feeding and swallowing difficulties which can adversely affect health.[3-5] Mastication problems may induce post swallow residue, which is known to lead to complications like choking and the perception of food stuck in the throat.[6-9] A possible cause of these problems appears to be related to deterioration of the masticatory function and therefore a deepened understanding of the prevalence and the mechanisms behind mandibular dysfunction in NMD is needed. This thesis aimed to contribute to these insights and improve quality of life of patients with SMA and DMD as well, and take first steps to develop interventions, such as training in DMD, to maintain adequate masticatory function as long as possible.

In this chapter the results of this thesis are discussed for each research question. The differences between SMA and DMD in clinical presentation and underlying mechanisms are addressed and the need for disease specific training is discussed. Training recommendations for SMA and DMD, methodological considerations, conclusions and suggestions for future research are provided.

PART I: Spinal muscular atrophy (SMA)

The Dutch patient organization noticed that a significant number of their members with SMA experienced a progressive restriction in mouth opening. The department of Oral-Maxillofacial Surgery, Prosthodontics and Special Dental Care at the University Medical Center Utrecht, the Netherlands was invited to investigate the mechanism behind this symptom and formulate an advice to their members.

1 What is the prevalence of impaired mandibular function in SMA?

The question of the SMA patient organization led to a master graduation project of two physiotherapists, followed by a pilot study in 12 children and adolescents with SMA type 2 compared to healthy subject (chapter 2). During this study, collaboration started with the department of Neurology at the UMC Utrecht and the department of Oral function and prosthetic dentistry and the department of Rehabilitation (rehabilitation medicine and speech therapy) at the Radboud university medical center, the Netherlands. The patients filled out 3 questionnaires regarding mandibular function; Screen, Mandibular Function Impairment Questionnaire (MFIQ) and Patient Specific Approach (see chapter 2). The participants underwent a clinical examination of the masticatory system. The study demonstrated that impaired mandibular function was common among young patients with SMA type 2; active maximum mouth opening with an aMMO ≤ 30 mm was present in 75% of the patients. Forty-five % of the patients with an aMMO ≤ 30 mm scored a low function impairment in the MFIQ, indicating a discrepancy between these limitations and the awareness of the patients, parents and care takers. Mild pain could be provoked in 2 out of 12 patients during traction and translation of the temporomandibular joint (TMJ) and in 8 out of 12 patients during assisted maximal mouth opening; no pain was reported in the control group. Pain is not characteristic for SMA and may be attributed to internal structure changes of the masseter muscle.[10] The pilot study made clear that there is a need to inform patients regarding the impact of SMA on the mandibular function.

Two additional SMA studies took place between July 2010 and July 2013 in patients who visited the outpatient clinic of the UMC Utrecht, the Netherlands.

Study A: the home visit study (chapter 3).

Patients with SMA type 2 and type 3, listed in the Dutch SMA registry were informed by letter to participate in a study of mandibular function. Sixty patients with SMA type 2 and 3 were examined through home visits.

Study B: cross-sectional study in 145 patients with SMA types 1-4 (chapter 4).

Patients with SMA types 1-4, listed in the Dutch SMA registry, were examined at the outpatient clinic of the University Medical Center Utrecht, the Netherlands. Measurement of the aMMO took place and in 12 patients muscle groups relevant for mouth opening and closing and mandibular condylar surface and condylar sliding were visualized by magnetic resonance imaging (MRI).

The cross-sectional study demonstrated an influence of SMA type on aMMO ($p < 0.01$). The reduced mouth opening was common in SMA types 1-3a. During the home visit study, the first research question was addressed more extensively by adding the variables bite force and the masticatory performance to the protocol of the pilot study. The questions in the Patient Specific Approach questionnaire overlapped with the questions in Screen and MFIQ; for this reason this questionnaire was removed from the protocol. The study demonstrated that all mandibular movements and the MVBF were significantly reduced in patients with SMA compared to the controls, with type 2 more affected by the disease than type 3a and 3b. The masticatory performance was not significantly different in the patient group compared with the control group, neither between the three SMA types. Masticatory performance is, next to bite force, primarily influenced by the number of functional tooth units (occlusal contacts) in healthy subjects.[11] Although there was a high percentage of (tendency to) cross bites in our patient group, the mean number of occlusal contacts (OC score) was only one occlusal contact lower than in the control group and is still sufficient to mix the wax tablets. Patients were asked to chew 20 times on the two-coloured wax tablet, which may be insufficient to capture fatigability, an important additional problem to weakness in patients with SMA.[12]

A reduced mouth opening may hamper oral hygiene and dental care. Inadequate oral hygiene is encouraging the bacteria colonizing in the oral cavity and dental plaque. Oral hygiene Gram-negative (anaerobic) bacteria in the oral cavity in frail elderly are reported to be a source of infection for aspiration pneumonia.[13] Since SMA patients are at risk of dysphagia, which is closely associated with aspiration pneumonia, oral hygiene is, like in frail elderly, an important issue in patients with SMA.[13-16] Control of oral biofilm formation by improved oral hygiene, reduces the numbers of potential respiratory pathogens in the oral secretions, which in turn reduces the risk for pneumonia .[17-19] To date, there is no definitive agreement about the most effective oral care protocol. Optimal measures of oral hygiene by brushing with regular toothbrush and rinsing with chlorhexidine mouthwash in critically ill patients are reported.[20]

2 Is the bulbar muscle function affected by SMA type 2 and 3?

Multiple linear regression analysis in the cross-sectional study in 145 patients with SMA types 1-4 revealed other determinants for aMMO than the home visit SMA study due to a difference in SMA types. In the home visit study, patients with SMA types 2 and 3 listed in

the Dutch SMA registry participated; in the cross-sectional study 145 patients with SMA types 1, 2, 3 and 4 were investigated.

In the home visit study the aMMO and the anterior MVBF were considered the main outcome variables. A striking finding is the correlation between the aMMO and the subjectively reduced mouth opening, which was not reported in the previously performed pilot study (chapter 2). This correlation may be due to the awareness of a reduced mandibular function in patients with SMA and their caretakers increased over the last 3 years, possible by informing the SMA patient organization and their members and thus a higher awareness after the pilot study was published. Multiple linear regression analysis revealed SMA type, MFIQ, difficulties in biting of food and food adaptation as determinants for reduced aMMO, SMA type, MFIQ, difficulties biting of food and food adaptation for a reduced anterior MVBF (chapter 2).

In this cross-sectional study, the determinants for reduced aMMO were SMA type, age, muscle weakness and dysphagia ($p < 0.05$). ROC curves were generated to analyze the predictive value of clinical motor scores and aMMO for the presence of dysphagia. Reduced aMMO reflect a more widespread process of degenerative changes of bulbar muscles and may represent an easy tool to assess the risk for dysphagia in patients with SMA, but this needs further study.

3 What is the underlying mechanism for the impairment of mandibular function in SMA?

To be able to fully open the mouth, both rotation and sliding of the mandibular must occur. Reduced sliding of the TMJ will lead to a reduction of aMMO. In chapter 2 we suggested that the reduced mandibular range of motion (ROM) of the patient group compared to that of the controls may be caused by changes in the morphology of the TMJ. Inadequate mandibular movement caused by a progressive weakening of mastication and neck muscles might initiate these changes. Magnetic resonance imaging (MRI) data from 12 patients with SMA type 2, 3 and 4 demonstrated in the 7 patients with the most severe reduction of aMMO (range 10–30 mm) evident atrophy and fatty infiltration of the lateral pterygoid muscle with only mild changes in other mouth opening muscles, i.e.digastric and geniohyoid muscle. This may provide an explanation of the pathophysiology of the reduced aMMO. Comparing MRI in open and closed mouth position revealed limitation of the condylar mobility. The mandibular condyles did not show structural changes of the articular surfaces. Degenerative changes of

the lateral pterygoid muscle, mediating mouth opening by condylar sliding, play an important role in the development of reduced aMMO, but other factors cannot be ruled out. Mild changes in the suprahyoid muscles such as contracture or degenerative changes with a resulting stiffness of the masticatory system may have a similar effect on the aMMO because of the longer distance between their bony insertions to the mandible and the TMJ. Although MRI sequences may detect bony changes, CT imaging is more appropriate than MRI for assessing structural changes of the articular surfaces of the TMJ.[21]

Surprisingly, masticatory performance was not significantly different in the patient group compared with the controls, neither between the three SMA types. The home visit study addressed the influence of bite force, but there are other aspects of mastication performance, particularly fatigability, that we have not addressed. In a previous study on skeletal muscles, the 6-minute walk test demonstrated a correlation between weakness and fatigue; longitudinally weakness did not change, but fatigue increased significantly.[12] Future studies on the role of fatigue in reduced mastication performance may consider an amended study design using the mixing ability index. Additional mixing ability assessments up to e.g. three sequential tests in one measurement session and time indication per test may show a difference in fatigability between patients with SMA and healthy controls. Another aspect that may be the subject of future research is how the recruitment of motor neurons is affected in reduced mastication performance.

PART II: Duchenne muscular dystrophy

Research support from Duchenne Parent Project was received to perform a pilot study on the prevalence and mechanisms of mandibular dysfunction related to DMD, and their relationship with swallowing problems (chapter 5 and 6). Part of this project was dedicated to the evaluation of masticatory training in patients with DMD (chapter 7).

4 What is the prevalence of impaired mandibular function in DMD?

Twenty-three patients, originating from a swallowing study of van den Engel-Hoek and co-authors at the department of Rehabilitation, Radboud university medical center, Nijmegen, the Netherlands, and 23 age and gender matched healthy controls were investigated during home visits, following the protocol described in chapter 3.[8] In the patients, quantitative muscle

ultrasound imaging (QMUS), a quantitative echo intensity analysis, of the tongue and motor function measurement (MFM) were added to the protocol. The MFM is collecting, among other items, information about the sitting position, arm function, and neck and head control.[22] Based on the ambulatory function of the patient and the MFM, patients were divided in three subgroups: early and late ambulatory stage (AS), early non-ambulatory stage (able to maintain posture, ENAS), or late non-ambulatory stage (upper limb function and postural maintenance is increasingly limited, LNAS) (chapters 5 and 6).[2]

The results of this study demonstrated a reduced masticatory performance, reduced bite force, high percentage of dental abnormalities (cross bite and tendency to cross bite) and prolonged mealtime as early signs of motor function deterioration, even before MFM changes became obvious in patients with SMA compared to healthy subjects. These early changes suggest that training of the mandibular function has to start early in the disease process. Mandibular movements were significantly reduced in the patient group compared to the controls but none of the patients reported problems with these limitations (chapter 5).

Limitations in the masticatory performance appear to be a dominant problem as reported by our patients with DMD in Screen and MFIQ (Chapter 5). Poor mastication of food in combination with weak pharyngeal clearance may increase pharyngeal post swallow residue and choking and possibly contribute to an increased risk of food aspiration.[3,6-8,23] In healthy dentate subjects, chewers with a low masticatory performance do not necessarily chew longer before swallowing than chewers with a high masticatory performance. As a consequence bad chewers in this healthy cohort would, on average, swallow larger food particles (Fontijn-Tekamp 2004).[24] To our knowlegde, there is no clear evidence or reports in the DMD literature of a correlation between poor mastication leading to swallowing large pieces of food and aspiration, hospitalizations and life-threatening pneumonia.

5 What are predictive factors for mandibular function in DMD?

Masticatory performance

To study the association between masticatory performance and each predictive factor, univariate linear regression analyses were performed. These analyses revealed a negative correlation between masticatory performance and DMD stage (ENAS), and the anterior MVBF. Because of the small number of patients only two variables were used in the multiple linear regression analysis, which indicated the stage of the disease as the strongest predictive

factor for masticatory performance ($R^2 = 0.52$).

Active maximum mouth opening

Univariate linear regression analyses for aMMO were performed and revealed negative correlations between aMMO and age, body height, ultrasound score of the digastric muscle and geniohyoid muscle, and positive correlations between aMMO and MFM. According to the multiple regression analysis MFM was the strongest predictive factor ($R^2 = 0.52$). The correlation between the aMMO and the MFM can be explained by the reported correlation between the muscular function of the cervical vertebral column and the mandibular function.[25,26] Patients with DMD develop a progressive cervical lordosis, rigid neck hyperextension and poor head control in their teens.[27-29] As MFM item 13 and 14 are designed to collect information about the head and neck control, the MFM score might be associated with aMMO. In chapter 6, the low scores on MFM item 13 and 14, mainly in patients classified as LNAS demonstrated the poor trunk position and head control. In this ambulatory stage 6 out of 10 patients (60%) had a limited mouth opening. We suggest that poor trunk position and head control may have an effect on the mandibular range of motion.

6 What is the underlying mechanism for the impairment of mandibular function in DMD?

Masticatory performance

The dominant factors influencing masticatory performance in healthy subjects are, as mentioned before, the number of occlusal contacts and the bite force.[30] Furthermore, tongue function is of importance because of its role in food-bolus mixing, formation and positioning.[31] In this study, the anterior MVBF, representing the strength of the mandibular closing muscles, and the number of occlusal contacts were significantly lower in patients with DMD compared to controls (chapter 5). A previous sonographic study indicated fatty infiltration related to the dystrophic changes of the masseter muscle in patients with DMD which explains the low anterior MVBF.[10] The occlusal changes expressed as (tendency to) cross bite, developed early in the course of the disease and is due to an increase in tongue thickness without structural changes in ENAS (hypotrophy) and later dystrophic change (i.e. the infiltration of fat and fibrous tissue, hypertrophy) of the transverse tongue muscle in LNAS.[8] The increased tongue thickness and dystrophic changes and weakness of the masseter

muscle in combination with the early occlusal changes play an important role in the development of a low masticatory performance in our study (chapter 5).

From the literature we know that a reduced range of hyoid movement in DMD patients was strongly associated with an increased risk of post-swallow residue.[23] Oral phase problems and post-swallow residue with solid food were observed, mostly in the LNAS.[8] We suspect that reduced masticatory performance leads to swallowing of larger pieces of food and an increased post-swallow residue. Because this residue is likely to spill into the open airway, it places patients at risk for aspiration pneumonia. A previous study reported medication use for pneumonia in 54% of the patients in the LNAS in the past year.[8] The missing link between poor mastication, swallowing large pieces of food and aspiration remains to be studied.

Mandibular range of motion

As mentioned earlier, sonography indicated degenerative changes related to the dystrophic changes of the masseter muscle and the suprahyoid muscles in DMD patients.[8,10] Muscle dystrophy may lead to muscle stiffness and consequently may hamper mouth opening and horizontal jaw movements as reported in chapter 5. Protrusion and mandibular ROM were reduced in patients compared to controls, although the reduction of protrusion and mandibular ROM leaves room for condylar sliding. This is confirmed by results of the clinical assessment of condylar movement capacity relative to the crest of the eminence: 80% of the patients with aMMO smaller than 35mm (4 of 5 patients) had a normal condylar sliding, and just 20% (one patient) had a limited sliding relative to the eminence crest. It seems that the TMJ is not involved. Whether the lateral pterygoid muscle is involved has not yet been investigated. MRI could reveal the influence of DMD on the lateral pterygoid muscle, as was reported in patients with SMA (chapter 4). Our results together with the observations reported in the literature about dystrophic changes of the masseter muscle and the suprahyoid muscles indicate that structural changes in the masticatory muscles may primarily be responsible for a reduced mandibular ROM in general, and for aMMO in particular.[8,10]

In conclusion, the results of this study illustrated that mandibular ROM and masticatory performance in DMD patients are significantly reduced compared to the healthy subjects; limitations of the masticatory performance as reported in the questionnaires were a dominant problem for patients with DMD.

7 What is the efficacy of training the masticatory muscles using chewing gum in DMD?

There is a lack of evidence for advising an appropriate exercise program for skeletal muscles as well as for masticatory muscles in patients with DMD.[2,32] Inappropriate activities may exacerbate the dystrophic process. On the other hand, reduced physical activity may lead secondary to ‘’disuse’’ muscle atrophy. The gold standard is a suitable monitoring of the balance between rest and activity.[33] A recent study in boys with DMD on the effect of assisted, low-intensity bicycle training on preservation of skeletal muscle endurance and functional abilities reported promising results.[35]

In healthy subjects, chewing during meals 3 times per day is considered optimal regarding the use of the masticatory muscles. But a reduced activity of masticatory muscles in healthy Japanese children through a preference for soft food, led to a decrease in muscle strength with a negative influence on the masticatory performance.[35,36] In DMD a reduced masticatory performance contributes to prolonged meal time and masticatory muscle fatigue. In the study described in chapter 5, patients in LNAS reported prolonged duration of food intake leading to weight loss and food adaptation. Food adaptation, defined as unable to eat hard biscuits, meat, raw carrots, French loaf or nuts, was reported in 52% of the patients with DMD, which is in agreement with other reports.[23] Eating soft and chopped food leads to underloading of the masticatory system, including the muscles of mastication. In DMD, also bite force is reduced compared to the healthy subjects, suggesting that the masticatory muscles are involved. Muscle training seems a possibility to reduce chances of deterioration or postpone detoriation of the masticatory muscles. A correlation was found between the MVBF and masticatory performance (chapter 5), offering a possibility for intervention in DMD.

Two studies in DMD investigated the effect of masticatory muscle training. The training program described by Kawazoe et al. improved the masticatory performance by means of jaw-clenching for 5 min. each time followed by mandibular and neck ROM exercises.[37] Another training program that included a therapist-assisted training twice a week, application of hot pack on the cheeks, massage of the masseter muscles, and (before each meal) self-training including passive stretching exercise by opening the mouth to the maximum degree, increased the bite force without influencing MMO.[38] The training of Kawazoe et al. does not match with the latest training suggestions for patients with muscular

dystrophy, which are low intensity aerobic exercises.[37] Moreover, clenching the jaws is difficult because of the early loss of bite force and the loss of the number of occlusal contacts, described in chapter 5. These limitations will limit the feasibility of the training of Kawazoe and coworkers[37]. Both studies do not fit in daily life routine and are too demanding for patients as training of the masticatory muscles should be continued as long as it is safe for the health of the patient.[37,38]

Although masticatory muscles are different in histology and functional properties compared to skeletal muscles, we decided to develop a training program inspired by the dynamic, active-assisted bicycle training performed by Jansen and co-authors in 2013.[34] Use of a soft type of chewing gum is a low intensity aerobic exercise, low resistant, easy to implement in daily life routine and common activity among youngsters which result in a good compliance. Furthermore the sugar free chewing gum used in this study contains xylitol, which improves oral health. The results in our study indicate that masticatory training by using sugar free chewing gum 4 weeks is indeed feasible and safe, and is improving the masticatory performance in the patient group. Because the bite force in our study did not improve, the working mechanism of the improvement in mastication performance may relate to changes of the neuromuscular function and coordination, resulting in improvement of skills in performing mastication.

PART III: Comparison, integration and implementation

I. What are the similarities between SMA and DMD?

Patients with SMA and DMD report both feeding and swallowing problems although the pathogenesis of each disease is distinct, and each disease has distinguishing characteristics.[3-5,39] Feeding problems are represented in patients with SMA and DMD by a reduced mandibular function (chapter 2–6). As described in chapters 2 to 6, the weakness of the masticatory muscles, dental malocclusions and reduced mandibular range of motion in combination with previously mentioned abnormal craniofacial growth patterns and reduced function of the tongue, are all involved in the development of mandibular dysfunction in both children and adults with SMA and DMD.[40-44]

Video fluoroscopic swallow studies showed that impaired swallowing leads to pharyngeal post swallow residue of solid food in advanced stages of SMA and DMD and increase in volume with age.[6,8,9,45] When large amounts of post swallow residue remain, the

risk for aspiration is increased when the patient inhales after the swallow and the airway opens naturally.[46] Food adaptation might start as soon as patients are concerned about food aspiration.

II. Are there differences between SMA and DMD in clinical presentation and underlying mechanisms in the masticatory system?

How much influence the muscular environment has on mandibular function depends of the origin of the NMD. Each type of NMD is showing specific signs and symptoms of impaired mandibular function. In SMA, mandibular dysfunction is induced directly via the bulbar motor neurons with secondary peripheral muscular sequels (chapters 3 and 4); In DMD, the pathophysiological substrate is located peripherally with primary affection of the muscles.

Although promising therapies are currently being developed there is still no cure for patients with SMA and DMD.[48] A difference between SMA and DMD is that the use of corticosteroids as a symptomatic treatment demonstrates beneficial effect on muscle strength and function in boys with DMD but no beneficial effect in SMA.[49,50]

In this thesis the answers in the questionnaires Screen en MFIQ, the range of motion tests of the mandible, MVBF and the chewing efficiency reveal differences in function of the masticatory system between SMA and DMD.

Spinal muscular atrophy

Chapters 3 and 4 provide further evidence for clinically relevant bulbar involvement in patients with SMA. Bulbar involvement leads to at least two dominant impairments of mandibular function, i.e. mandibular ROM and MVBF are diminished in patients with SMA types 2 and 3. The fatty degeneration of the lateral pterygoid muscle is playing an important role in the development of a reduced aMMO but other factors cannot be ruled out. Weakness of neck muscles may further contribute to impaired mandibular function. Head retraction by the neck muscle in an attempt to stabilize the balance of the head may increase reduction of the opening capacity of the mouth (chapters 2 and 3).[45] Our data support a model for mandibular dysfunction caused by gradually increasing weakness of muscles that mediate mouth opening and closing, leading to MVBF reduction and development of progressive contractures of the TMJ.

Because of the relatively high percentage of our patients who report problems with chewing it was somewhat surprising that masticatory performance did not differ between

patients and control groups. Although mastication performance was maintained, the MVBF was reduced in the patients compared to the controls, more in SMA type 2 than type 3a and 3b.The mixing ability index in our studies measured 20 chewing strokes, which does not include fatigability. It is advised to address the fatigability issue in future studies.

Duchene muscular dystrophy

In DMD, the masticatory performance is the dominant impairment with disease severity as the strongest predictive factor for masticatory performance.

MVBF, number of occlusal contacts and masticatory performance in DMD are severely reduced. It is probably the combination of an enlarged tongue, weakness of the masseter muscle, expressed by a decrease in MVBF early in the disease process that cause the loss of number of occlusal contacts. The loss of occlusal contacts in combination with a reduced anterior MVBF is playing an important role in the development of a reduced masticatory performance in boys and man with DMD.

We cannot determine whether the decline in masticatory performance or the efficacy of the chewing training in the patients with DMD was further influenced by exposure to prednisone (chapters 5 and 7). Prednisone-naïve DMD patients are insufficiently represented in ambulatory stage and early non-ambulatory stage to assess a statistical link between prednisone and masticatory muscle function. Additionally, the standard of care for DMD has changed overtime, resulting in a different standard of treatment for older compared to younger patients.

III. Is there a need for specific training advice for SMA and DMD?

The studies in this thesis demonstrated that there is a need for a specific training program for SMA and for DMD patients. Mandibular function, expressed as mandibular ROM, masticatory performance and MVBF, were different in their presentation due to the distinct pathology and characteristics of each disorder. Very likely each NMD e.g. myasthenia gravis, myotonic dystrophy, congenital myopathies will present disease specific symptoms of the mandibular function and need a desease specific training program. Each NMD requires a tailored approach to help the patient to cope with the encountered difficulties he / she is posed for and to delay the process of deterioration.

IV. Which disease-specific recommendations for training protocols can be given in SMA and DMD?

Because of the complexity of the disorders, patients with SMA and DMD have to be treated within a multidisciplinary setting. Different impairments are influencing each other, like sitting position, head balance, swallowing and respiratory function. In order to integrate stimulation of the masticatory system in rehabilitation and modern management of complications a safe feeding plan has to be present. The multidisciplinary team should consist of e.g. orthopedic surgeon, pulmonologist, cardiologist, dentist, physiotherapist, occupational therapist, speech therapist, dietician, and social worker.

For specific recommendations for SMA and DMD explorative cross-sectional research with larger groups is needed to study the mechanisms behind the impairments of the mandibular function. After the cross-sectional studies randomised clinical design studies are required. Until RCT data are available; we only can make suggestions for training of the mandibular system.

For both SMA and DMD in the non-ambulatory stage of the disease, the complications of dysphagia and weight loss, due to pronged meal time, lead to food adaptation.[4,5,20,51,52] Since there are no cut-off values for aMMO and mixing ability, when effecting swallowing negatively, the decision to adapt food should be based on sufficiency of the airway defense mechanisms, cough strength and calorie intake, which falls under the care of the medical specialist. Education of patients, parents and caretakers, making them aware of the probability of a limited mandibular function, must be an integral part of the total care in SMA and DMD.

Spinal muscular atrophy

In SMA, the main limitation of the mandibular function is the mandibular ROM and the MVBF. We suggest that a training protocol has to focus on active movements and stretching, and be easy to implement in daily life in combination with keeping the maticatory system active. Advised physical exercises include passive stretching of the mouth opening and passive movement of the mandible in all horizontal directions. The timing of therapeutic passive stretching exercises and its effectiveness, once severe limitation of the mandibular ROM is present, remain unclear. Based on MRI information and clinical experience, the training can start when the patient is still in the ambulatory stage, before muscle involvement has progressed to an irreversible stage (Table 8.1).

Duchene muscular dystrophy

In DMD, the main limitation of the mandibular function is the masticatory performance. We suggest that a training protocol has to focus on training mastication with low intensity aerobic exercises. The training should be easy to implement in daily life. Our findings advocate the advice to encourage patients with DMD to postpone food adaptation as long as the airway defense mechanisms, cough strength and calorie intake are sufficient. If food adaptation is a necessity for quality and duration of life, food adaptation needs to take place. The suggestion applies mainly to patients in the early and late ambulatory stage and the early non-ambulatory stage of the disease because patients in these two groups usually meet these requirements. In case the requirements are not met, the suggestions of van den Engel-Hoek et al. (2013) are relevant: (1) adjust meals in terms of less solid food and (2) drink water after meals to clear the oropharyngeal area.[8] Moreover, we suggest that masticatory exercises (chapter 7) are applied in DMD as early as possible in the disease. For example, at first reports of food adaptation, in an effort to postpone the decline of masticatory muscle function in these patients (Table 8.1).

Table 8.1. Recommendations for mandibular function training in patients with SMA and DMD

SMA	**DMD**
Treat the patient within a multidisciplinary setting to integrate stimulation of the masticatory system in a safe feeding plan.	
Keep the masticatory system active by eating (semi) solid food Airway defense mechanisms, cough strength and calorie intake must be sufficient.	
Start physical exercises of the masticatoy system as early as possible.	When adjustment to a soft diet has to take place, start mastication training.
Physical exercise: stretching of the mouth opening and active movement of the mandible in all horizontal directions.	Mastication training: one piece of soft sugar free chewing gum per exercise, 3 x / day, 30 min / session, 5 days / week.

Reflection on clinical outcome measures

In this thesis, first we described the main parameters expressed as mandibular ROM, the anterior MVBF and the masticatory performance, to assess the mandibular function. Second, we discussed the medical data of the motor function from the department of rehabilitation of the Radboud university medical center, Nijmegen and the department of Neurology and Neurosurgery and Spieren voor Spieren Kindercentrum, University Medical Center Utrecht, the Netherlands.

Mandibular ROM

Suggested cut-off values for reduced aMMO in population based studies vary between 40 – 44 mm for men, 38–42 mm for women and 35–38 mm for and for horizontal movements of the mandible (protrusion, right and left lateral movements) is 5–8 mm.[53-58] In view of the wide range of variation of individual mandibular movements due to e.g. anthropologic factors, morphology and status of the masticatory system it is not practical to suggest cut-off values for mandibular ROM per age category.[11,56, 59,60] Moreover, the range of motion always needs to be evaluated in the full context of the patient. In this thesis the values of the mandibular movements are discussed as reduction of the mandibular movements compared to healthy controls rather than as cut-off values.

Anterior maximum voluntary bite force

When measuring MVBF in human subjects, the reliability of the measurements within subject and between sessions differed considerably in previous studies.[61] In longitudinal studies, the total reliability, after controlling for age, was better for incisor MVBF than for molar MVBF.[61] The measurement of anterior MVBF between the upper and lower canines is not always feasible because of loose, partly erupted or missing canines, due to changing from primary to secondary dentition. The posterior MVBF may be severely complicated or impossible due to e.g. reduced mouth opening, posterior cross bites, and loss of contact in the molar region. With reference to these complications, during assessment of MVBF in this and in future longitudinal research, the MVBF needs to be measured between the upper and lower central incisors.

Masticatory performance

In the majority of the studies on masticatory performance, the degree of breakdown of food

has been determined by sieving the food particles. A natural test food has the advantage that it is normally consumed, so that subjects are accustomed to it.[11] In our vulnerable patient groups with an increased risk of aspiration, we decided to use wax tablets which form a homogeneous bolus after mastication. In the literature it has been suggested to offer the wax tablet at a higher temperature in patients with severely compromised masticatory performance.[62] Prior to the start of the study, we offered tablets at a temperature of 30 °C to three subjects. Under these conditions, pieces of wax were sticking to the teeth and a coherent bolus could not be collected which lead to the decision to offer the wax tablets at room temperature. As an alternative for the mixing ability test a two-colour chewing gum test for assessment of masticatory performance could be used.[63]

Motor function

Multidisciplinary setting of this thesis allowed combining of medical and dental data. One of the medical variables we used was the motor performance of the patients. Different tools for assessment of motor performance are used in a variety of medical settings like in our study. At the department of Rehabilitation of the Radboud university medical center, Nijmegen, the Netherlands, the Motor Function Measure (MFM) is used and at the department of Neurology and Neurosurgery and Spieren voor Spieren Kindercentrum, University Medical Center Utrecht, Utrecht, the Netherlands, the Expanded Hammersmith Functional Motor Scale (HFSME) is used to assess the motor function in patients with NMD. MFM and HFSME are both validated scales and can be used in SMA and DMD.[22,64] Apart from items also present in HMFSE, MFM includes items on head balance including neck function, and sitting balance in relation to head positioning. These items showed a strong association with our results.

Methodological issues

Case-control studies are particularly appropriate for studying rare diseases since they start with including diseased individuals. This selection allows for enrolment of a sufficient number of patients. We have to realize that case-control studies may prove an association but they do not demonstrate causal relationships. The conclusions made in this thesis raise questions that can be investigated in longitudinal studies and hypotheses to be tested in RCT's.

Future perspectives

Some of the following future perspectives have been mentioned in the general discussion previously. In this final section a brief summary of these perspectives is presented.

In rare diseases, such as NMD, the evidence available for clinical guidance and decisions regarding the masticatory system is often lacking. SMA and DMD share many challenges with other rare diseases, such as limited access to resources required to start a clinical trial (including collaborations and funding), and difficulties of recruiting a sufficient number of patients. Solutions to these barriers will require multicentered and perhaps multinational collaboration, partnership with patient organizations, training of a new generation of researchers interested in NMD, and organising funding.

Future research in SMA and DMD is needed to investigate the efficacy of a training of the mandibular function that prevents progression using a randomized controlled design. Because of two existing databases in the Netherlands for patients with SMA and for patients with DMD, a randomized controlled design study may be possible. Cut-off values for masticatory performance or bite force acting as indicators for the timing to adjust food consistency in routine NMD clinical practice are missing. There is a need for establishing these values in order to improve clinical practice. Fatigability is a frequent complaint in SMA as well as in DMD and may play a role in the reduction of mandibular function due to tiredness and loss of strength of the masticatory muscles during function.[65] The pathophysiology of fatigability is not entirely clear. It may be due to e.g. (1) reduction in the initial median frequency, probably because of the reduced number of motor units, (2) specific fatigue impairment at a muscle fiber level because of the greater activation required to achieve a desired muscle force, (3) failure of central activation as a result of reduced motivation or fear of physical activity, (4) central nervous system adaptations following disuse, or (5) reduced sensory input with movement.[34,66-68] Not only fatigability but also endurance are aspects of muscle function and must be taken into consideration in future training studies.

The collaboration between the various departments involved in this study has improved the knowledge of the underlying mechanisms of an impaired mandibular function in SMA and DMD, but there are still unanswered questions. Future research has to focus on the association between limitations of the mandibular function and swallowing problems. The correlation between mandibular dysfunction, swallowing problems and aspiration, hospitalizations and life-threatening pneumonia is unclear when taking anatomy and

physiology into account; the exact mechanisms behind the impairments need to be clarified in order to improve oral function and swallowing in patients with DMD and SMA. Longitudinal evaluation of aMMO in order to predict the need for training in the various disease categories is needed.

Conclusions

In summary, the conclusions from this thesis are:

- There is a clinically relevant difference between the measured outcomes of mandibular function in SMA and DMD compared to healthy subjects.
- In SMA the dominant impairments of the mandibular function are the mandibular range of motion and bite force; in DMD the dominant impairment of the mandibular function is the masticatory performance.
- Reduced mouth opening in patients with SMA type 2 is primarily induced by selective fatty infiltration of the lateral pterygoid muscles.
- In order to establish the need for training in the various disease categories, longitudinal evaluation of mandibular function is a necessity.
- There is a need for disease-specific training programs for patients with SMA and DMD.

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Chapter 9

Summary

Neuromuscular disorders are defined as a wide range of chronic degenerative diseases associated with severe muscle weakness, which also affect the masticatory muscles. Two of the most common types of neuromuscular disorders are spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD). Structural changes and weakness of the masticatory muscles and impaired tongue function may cause specific abnormalities in mandibular function. As SMA and DMD have its distinct pathophysiology, each disorder may have a different impact on the masticatory system.

The primary aim of this thesis was to explore the impact of SMA and DMD upon aspects of mandibular function of patients with SMA and DMD focusing on mastication and mandibular mobility. The second aim was to establish whether the differences in pathophysiology and clinical presentation of SMA and DMD cause distinct patterns of compromised mandibular function. A third aim was to investigate whether specific training provides a positive impact on masticatory function in DMD.

The aim of **chapter 2** was to investigate the mandibular function in 12 patients with SMA type 2 compared to a matched control group. Participants completed questionnaires about mandibular function and underwent a clinical examination of the masticatory system. Fifty percent of the patients reported a moderate to severe impairment of the mandibular function. An active maximum mouth opening (aMMO) less than or equal to 30 mm was observed in 75% of the patients. In patients with a severe reduction of the mandibular range of motion, the temporomandibular joint mainly rotated during mouth opening instead of the usual combination of rotation and sliding. The severity of the limited aMMO correlated with the severity of the disease, expressed as motor function measurement (MFM). This study demonstrated that mandibular dysfunction is common amongst 6 to 19 years old patients with spinal muscular atrophy type 2.

Chapter 3 describes an investigation on the mandibular function, as reflected by masticatory performance, mandibular range of motion, and bite force in 60 patients with SMA type 2 and 3. Participants completed questionnaires about mandibular function. In addition, some predictors of mandibular dysfunction were explored. Patients with SMA type 2 and 3 showed significant impairment of mandibular movements compared to healthy controls ($p < 0.001$). Maximal bite force was 19% lower in patients than in controls. SMA type and neck muscle strength were relevant determinants of these complications. In this study further evidence for clinically relevant bulbar involvement evolved from the reduced mobility and bite force presented by the SMA type 2 and 3 patients.

In the study described in **Chapter 4** the prevalence of reduced aMMO was determined and its association with dysphagia, as a sign of bulbar dysfunction, was analyzed. A cross-sectional study of aMMO in 145 patients with SMA types 1-4 and 119 healthy controls was performed and used Magnetic Resonance Imaging (MRI) in 12 patients to visualize mandibular condylar shape and sliding and the tissue characteristics of muscle groups relevant for mouth opening and closing. aMMO ≤ 35 mm was found in 100, 79, 50 and 7% of patients with SMA types 1, 2, 3a and 3b/4, respectively and in none of the healthy controls. MRI showed severe fatty degeneration of the lateral pterygoid muscles that mediate mouth opening by initiating mandibular condylar sliding, but relatively mild fatty degeneration of the mouth closing muscles in patients with reduced aMMO. Reduced aMMO was associated with SMA type, age, muscle weakness and dysphagia. Reduced aMMO is a sign of bulbar dysfunction in SMA.

Chapters 5 and 6 describe two studies on mandibular function in 23 patients with DMD, aged 5 – 38 years and matched with 23 healthy subjects. Participants completed two questionnaires about mandibular function, underwent a clinical examination of the masticatory system and measurements of anterior bite force and masticatory performance. In addition, quantitative ultrasound of the tongue, the digastric muscle and the geniohyoid muscle and MFM was performed in the patient group. The patients were categorized into ambulatory stage (early or late, AS), early non-ambulatory stage (ENAS), or late non-ambulatory stage (LNAS).

Compared to the controls masticatory performance, anterior bite force and number of occlusal contacts were reduced in the patient group (all $p < 0.001$) (**Chapter 5**). Mastication abnormalities were present early in the disease process prior to a reduction of MFM. The early non-ambulatory and late non-ambulatory stage groups showed less masticatory performance compared to the ambulatory stage group ($p < 0.028$ and $p < 0.010$, respectively). Multiple linear regression analysis revealed that the stage of the disease was the strongest independent predictive factor for the masticatory performance ($R^2 = 0.52$).

In the patient group all mandibular movements were reduced ($p < 0.001$) compared to the controls (**Chapter 6**). Reduced aMMO (< 40 mm) was found in 26% of the patient group. LNAS patients had significantly smaller mandibular movements compared to AS and ENAS ($p < 0.05$). Multiple linear regression analysis for aMMO revealed a positive correlation with the body height and disease progression, with MFM score as the strongest independent predictive factor ($R^2 = 0.71$). Mandibular movements in DMD are significantly reduced and

become more hampered with loss of motor function, particularly in relation to the sitting position, arm function, and neck and head control.

The efficacy of mastication training in DMD using chewing gum for 4 weeks was determined in the study described in **Chapter 7**. Masticatory performance and bite force were assessed in 17 patients and 17 healthy age-matched males before, shortly after and one month after a specific mastication training program. In the patient group masticatory performance improved and remained improved after one-month follow-up, but no significant changes in anterior maximum bite force were observed after mastication training. In the healthy subjects bite force increased and remained increased at one month follow-up without significant changes in masticatory performance. It was concluded that mastication training, using sugar free chewing gum improved masticatory performance in DMD patients. Since bite force did not improve, the working mechanism of action of the improvement in chewing efficacy may relate to changes of the neuromuscular function and coordination

The research questions posed in chapter 1 are discussed in **Chapter 8**, including differences between SMA and DMD patients in their clinical presentation and underlying mechanisms. Also masticatory training recommendations for SMA and DMD are presented.

In conclusion, we found clinically relevant differences between mandibular function in SMA and DMD compared to healthy subjects. Differences in pathophysiology in SMA and DMD led to specific signs and symptoms of impaired mandibular function. The dominant limitation of the mandibular function in SMA was the mandibular range of motion and the bite force; in DMD this was the masticatory performance. In SMA, reduced mouth opening was primarily induced by selective fatty infiltration of the lateral pterygoid muscles. In DMD, mastication abnormalities were present early in the disease process prior to a reduction of motor function of the upper part of the body and was associated with the stage of the disease. Furthermore we noted a need for disease-specific training programs for patients with SMA and DMD. Until randomized clinical trials (RCT's) are available, only suggestions for training of the mandibular system can be made. It is advised to encourage SMA and DMD patients to postpone food adaptation as long as it is medically safe. In SMA, we suggest that training starts when the patient is still in the ambulatory stage, focusing on active and passive movements of the mandible in vertical and horizontal directions; in DMD, training should start as early as possible in the disease, at first reports of food adaptation and has to focus on training mastication with low intensity aerobic exercises. Explorative cross-sectional research with larger groups is suggested to study the mechanisms behind the impairments of the

mandibular function and develop further specific recommendations for SMA and DMD. After these cross-sectional studies randomised clinical design studies are required.

Chapter 10

Samenvatting in het Nederlands

(Summary in Dutch)

Neuromusculaire aandoeningen zijn syndromen en ziekten die de spieren en hun aansturing beïnvloeden. Op de voorgrond tredende symptomen zijn progressieve spierzwakte en verminderd fysiek uithoudingsvermogen. De twee meest voorkomende neuromusculaire aandoeningen zijn Duchenne musculaire dystrofie (DMD) en spinale musculaire atrofie (SMA). DMD wordt veroorzaakt door een mutatie van het dystrofine gen gelokaliseerd in het X-chromosoom. Dit veroorzaakt een tekort aan het eiwit dystrofine, nodig voor de stevigheid van de spiercelwand; de spiercellen beschadigen, sterven op den duur af, vervetten en bindweefsel komt hiervoor in de plaats. SMA wordt doorgaans veroorzaakt door deletie of genconversie in het 'survival'-motorneuron (SMN) 1-gen, waardoor degeneratie van de motorische voorhoorncellen in het ruggenmerg optreedt. Deze degeneratie beïnvloedt het signaal naar de spieren negatief. De spieren worden geleidelijk dunner en zwakker. Bij SMA en DMD blijken ook de spieren van het kauwstelsel te zijn betrokken, waardoor de mandibulaire functie gecompromitteerd kan zijn. Ondanks het veelvuldig vermelden van problemen met het eten, zijn de onderliggende mechanismen van een beperkte mandibulaire functie nauwelijks in kaart gebracht en de tandheelkundige behandelopties m.b.t. mandibulaire disfunctie vrijwel onbekend.

Het globale doel van het in dit proefschrift beschreven onderzoek was het onderzoeken van de mandibulaire functie bij mensen met SMA en DMD in vergelijking met gezonde mensen en de daaraan gerelateerde voorspellende factoren. Het tweede doel was om vast te stellen of de verschillen in pathofysiologie en klinische presentatie van SMA en DMD een karakteristiek onderliggend mechanisme van mandibulaire disfunctie laten zien. Bij mensen met DMD is bovendien gekeken naar de effectiviteit van een kauwtraining.

Het doel van **hoofdstuk 2** was het onderzoeken van de mandibulaire functie bij 12 patiënten met SMA type 2 die werden gematched met gezonde personen. Deelnemers vulden vragenlijsten in over mandibulaire functie en ondergingen een klinisch onderzoek van het kauwstelsel. Vijftig procent van de patiënten rapporteerde een gemiddelde tot ernstige beperking van de mandibulaire functie. Een actieve maximale mondopening (aMMO) kleiner of gelijk aan 30 mm werd gezien bij 75% van de patiënten. Bij de mensen met een ernstig beperkte aMMO liet het kaakgewricht tijdens het openen van de mond een rotatiebeweging zien in plaats van de gewoonlijk gecombineerde rotatie en translatie. Dit zou kunnen wijzen op een structurele verandering in het kaakgewricht. De ernst van het ziektebeeld, weergegeven als motorische vaardigheid, liet een associatie zien met een gereduceerde aMMO in vergelijking met de controlegroep. De uitkomsten van dit onderzoek maakten

duidelijk dat vervolgonderzoek wenselijk is bij een grotere patiëntengroep met verschillende typen SMA.

Hoofdstuk 3 beschrijft de invloed van SMA type 2 en 3 op de mandibulaire functie bij 60 patiënten, weergegeven als het kauwvermogen, de mandibulaire bewegingen en de bijtkracht. Deelnemers vulden vragenlijsten in over mandibulaire functie. Aanvullend werden de voorspellende factoren van mandibulaire disfunctie onderzocht. Het onderzoek toonde aan dat de aMMO, de laterale en proale bewegingen van de onderkaak en de bijtkracht beperkt waren ten opzichte van de controle groep ($p < 0.001$). Voorspellende factoren voor deze beperkingen waren het SMA type en de sterkte van de nekspieren. Het kauwvermogen, bepaald met een kauwtest bij patiënten en de controlegroep, was vergelijkbaar. Het onderzoek droeg bij aan aanvullend bewijs voor bulbaire betrokkenheid bij patiënten met SMA type 2 en 3.

In het onderzoek beschreven in **hoofdstuk 4** werden de prevalentie van een verminderde aMMO, de onderliggende mechanismen en de associatie tussen een beperkte aMMO en slikproblemen bepaald. Het onderzoek werd uitgevoerd bij 145 patiënten met SMA type 1-4 en 119 gezonde controles; bij 12 patiënten werd een MRI genomen om het oppervlakte, de proale beweging van het kaakkopje en de anatomie van spiergroepen, relevant voor het openen en sluiten van de mond, te visualiseren. Een aMMO kleiner of gelijk aan 35 mm werd vooral gezien bij SMA type 1-3a. De beperking werd vooral veroorzaakt door vervetting van de m. pterygoideus lateralis die mede verantwoordelijk is voor de mondopening door de kaakkop naar voren te trekken. Een mondopening kleiner of gelijk aan 35 mm was geassocieerd met het SMA type, de leeftijd, spierzwakte en slikproblemen en is een teken van bulbaire disfunctie bij SMA.

Hoofdstuk 5 en 6 beschrijven twee onderzoeken waarin de mandibulaire functie bij 23 patiënten met DMD in de leeftijd van 6 tot 38 jaar werd onderzocht en vergeleken met die van gezonde personen. Deelnemers vulden twee vragenlijsten in over mandibulaire functie, ondergingen een klinisch onderzoek van het kauwstelsel en metingen van bijtkracht en kauwvermogen. Daarnaast werd in de patiëntengroep kwantitatieve echografie van de tong, m. digastricus en de m. geniohyoideus uitgevoerd en werden de motorische vaardigheden bepaald. De patiënten werden in drie groepen verdeeld op basis van de fase van hun ziekte: vroege en late loopfase (fase 1, n=6), vroege rolstoelfase (fase 2, n=7) en late rolstoelfase (fase 3, n=10).

Het kauwvermogen, de bijtkracht en het aantal occlusale eenheden in de patiëntengroep waren sterk gereduceerd ten opzichte van de controle groep (alle $p < 0.001$) Deze veranderingen waren al vroeg in het ziekteproces aanwezig, nog voordat reductie van de motorische vaardigheden zichtbaar was (**Hoofdstuk 5**). De fase waarin de ziekte zich bevindt, was de voorspellende factor voor het kauwvermogen.

In de patiënten groep bleken alle mandibulaire bewegingen gereduceerd ($p < 0.001$) in vergelijking met de controle groep (**Hoofdstuk 6**). Bij 26 % van de patiënten werd een aMMO < 40 mm waargenomen. LNAS patiënten vertoonden een significant gereduceerde mandibulaire beweging in vergelijking met AS and ENAS patiënten ($p < 0.05$). Meervoudige lineaire regressieanalyse liet een positieve associatie zien tussen aMMO en lichaamslengte, en aMMO en ziekteprogressie waarbij de motorische vaardigheid de sterkste onafhankelijke variabele was ($R^2 = 0.71$). Beperkingen van de aMMO namen toe met het afnemen van motorische vaardigheden, inclusief de vastgestelde afname van de rompstabiliteit (positie van het zitten), de armfunctie en nek- en hoofdcontrole.

De effectiviteit van een 4 weken durende kauwtraining met suikervrije kauwgom in DMD werd vastgesteld in het onderzoek dat is beschreven in **hoofdstuk 7**. Bij 17 patiënten en 17 gezonde personen werd het kauwvermogen en de bijtkracht bepaald direct vóór, direct na en één maand na de training. De kauwtraining liet bij patiënten met DMD een verbetering zien van het kauwvermogen en deze verbetering hield aan tot tenminste één maand na de training. Er werden echter geen significante veranderingen in de bijtkracht waargenomen na de kauwspiertraining. Bij de gezonde personen nam de bijtkracht toe en die bleef verhoogd na een maand follow-up zonder significante veranderingen van het kauwvermogen. Concluderend mag worden gesteld, dat training van het kauwstelsel met behulp van suikervrije kauwgom het kauwvermogen bij patiënten met DMD verbeterde. Aangezien de bijtkracht onveranderd bleef, kan het werkingsmechanisme van de verbetering van het kauwvermogen toegeschreven worden aan neuromusculaire veranderingen en verbeterde coördinatie, hetgeen resulteerde in verbetering van het kauwen, vastgesteld met de mixing ability test.

De onderzoeksvragen en antwoorden van dit proefschrift worden bediscussieerd in **hoofdstuk 8**. Verschillen tussen patiënten met SMA en DMD ten aanzien van de klinische presentatie en de onderliggende pathofysiologische mechanismen van mandibulaire disfunctie worden aangegeven. Ook worden suggesties gegeven voor oefeningen gericht op behoud van de mandibulaire functie.

Uit dit onderzoek kan worden geconcludeerd dat er een klinisch relevant verschil in mandibulaire functie is tussen patiënten met SMA en DMD. Verschillen in pathofyiologie in SMA en DMD leiden tot specifieke tekenen en symptomen van mandibulaire disfunctie. Bij patiënten met SMA waren de voornaamste beperkingen de mandibulaire bewegingen en de bijtkracht en bij patiënten met DMD was dit het kauwvermogen. In SMA werd de beperking van de mondopening vooral veroorzaakt door vervetting van de m. pterygoideus lateralis. In DMD speelden de verzwakte kauwspieren en een reductie van de occlusale eenheden een rol bij het ontstaan van een beperkt kauwvermogen. Bovendien is er behoefte aan ziekte-specifieke trainingsprogramma ’s voor patiënten met SMA en DMD. Totdat gerandomiseerde en gecontroleerde onderzoeken (RCT’s) beschikbaar zijn, kunnen alleen suggesties gegeven worden voor het trainen van het kauwstelsel. Patiënten met SMA en DMD wordt geadviseerd om het kauwstelsel actief te houden door het aanpassen van voedsel zo lang mogelijk uit te stellen mits dit medisch verantwoord is. Training bij SMA patiënten zal gericht moeten zijn op het rekken van de mondopening en het actief bewegen van de onderkaak in het horizontale vlak (lateraal en proaal). De training kan starten in de vroege ambulante (loop) fase van het kind. Training bij DMD patiënten zal gericht moeten zijn op het kauwvermogen, voornamelijk middels een kauwtraining met een lage intensiteit. Aangeraden wordt om zo vroeg mogelijk met de kauwtraining te beginnen, zodra patiënten ervaren dat zij hun voedsel moeten aanpassen. Exploratief cross-sectionele onderzoeken van de mandibulaire functie in grotere groepen patiënten en gerandomiseerd onderzoek met een controlegroep zijn nodig om ziektespecifieke trainingsprogramma's voor SMA en DMD te ontwikkelen.

Dankwoord (acknowlegdements)

Curriculum Vitae

List of publications

Abbreviations and glossary of terms

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Curriculum Vitae

Harriëtte Willemijntje van Bruggen is op 7 april 1961 geboren in Groningen. Haar jeugd bracht zij door in Haarlem en Heemstede om aansluitend naar Groningen terug te keren om de opleiding botanisch analiste te volgen. Daarna studeerde zij van 1983 tot 1988 tandheelkunde aan de universiteit van Groningen om vervolgens te vertrekken naar Birchington-on-Sea in het noord- oosten van Kent, Engeland. Naast de werkzaamheden als algemeen practicus zorgde het behandelen van bijzondere zorggroepen in tehuizen voor een blijvende interesse in de bijzondere tandheelkunde. In 1995 verhuisde het jonge gezin terug naar Nederland. Na een korte periode werkzaam te zijn geweest bij het Centrum Bijzondere Tandheelkunde Rijnmond in Rotterdam werd wederom de oversteek gemaakt naar Engeland. De drie jarige opleiding bijzondere tandheelkunde aan het Eastman Dental Institute in Londen werd gevolgd. Terug in Nederland volgde zij naast het werken als algemeen practicus in Wassenaar, de opleiding tot tandarts-gnatholoog in Utrecht waar zij in aanraking kwam met mensen met een spierziekte. De afdeling gnathologie verhuisde naar het Radboudumc en het inmiddels gestarte onderzoek verhuisde mee. Het docentschap bij de afdeling gnathologie werd gecombineerd met het schrijven van aanvragen bij fondsen en het opzetten van samenwerkingsverbanden tussen UMC Utrecht en Radboudumc. Daarnaast werd tijd besteed aan het opzetten van een multidisciplinair team jeugdreuma (Radboudumc) en het opzetten van een screeningsmethode voor betrokkenheid van het kaakgewricht bij jeugdreuma (UMC Utrecht). Door het verwerven van financiële ondersteuning via het Duchenne parent project en de Cornelia stichting kon het onderzoek “mandibulaire functie bij neuromusculaire aandoeningen” in 2011 officieel van start gaan.

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Abbreviations

Abbreviations used throughout this thesis

aMMO	Active maximum mouth opening
AS	Ambulatory stage
DMD	Duchenne muscular dystrophy
EI	Echo intensity
ENAS	Early non-ambulatory stage
HFMSE	Hammersmith functional motor scale expanded
LNAS	Late non-ambulatory stage
MFIQ	Mandibular function impairment questionnaire
MFM	Motor function measure
MRI	Magnetic resonance imaging
aMVBF	Anterior maximum voluntary bite force
N	Newton
NMD	Neuromuscular disorders
OC	Occlusal contacts
pMMO	Passive maximum mouth opening
QMUS	Quantitative muscle ultrasound imaging
ROM	Range of motion
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
TMD	Temporomandibular disorders
TMJ	Temporomandibular joint
VAS	Visual analogue scale
VFSS	Videofluoroscopic swallow study